SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 87 JULY, 1948 NUMBER 1

THE STUDY OF PERIPHERAL VASCULAR DISEASE WITH RADIOACTIVE ISOTOPES — PART I

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THE objective measurement of blood flow has interested innumerable investigators. Many methods, while crude, have contributed to our understanding of the circulation. With the development of more exact instruments for such evaluation, the appraisal of circulatory disturbance has become more critical. These studies not only supplement clinical evaluation of the patient, but permit a more objective evaluation of symptoms, circulatory insufficiency, and results of various forms of therapy.

Investigation of circulatory physiology by instruments has previously been concerned with alterations in skin temperatures, changes in the volume of the extremity determined by the rate and volume of blood flow as measured by the plethysmograph, and dimensional pulsation of mass as determined by the oscillometer. These observations, while of value, reveal little in regard to the adequacy of the circulation in maintaining normal metabolism in the tissue of the extremity.

In man the flow of blood in the extremities is largely concerned with two factors: (1) the metabolic demands of the tissues, and (2) the regulation of body temperature. Since separate requirements of both are to be satisfied, it would be suspected that the mechanism of their individual accomplishment would be different. The effective circulation in the muscles of the extremities is dependent upon the flow of blood through the capillaries. In this manner the metabolic demands of the tissues are supplied and the waste products are removed.

Temperature regulation, on the other hand, is basically dependent upon variations in rate and volume of blood flow through the superficial channels. Sucquet and Hoyer described the neuromyoarterial glomus, which in man occurs chiefly in the distal part of the extremities. These structures effect arteriovenous anastomoses by permitting an opening between the terminal arteries and the veins of the extremities. When these anastomoses open, an increase in the skin temperature results. Harpuder and others have shown that when blood is shunted through such arteriovenous channels a deprivation of blood flow through the nutrient capillaries results, and tissue metabolism may be adversely affected. Therefore a rise in skin surface temperature is not an indication of an increase in the nutritional efficiency of the circulation in a part. Similarly, changes in volume of the extremity as measured by the plethysmograph are to be expected with the opening of the

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This work was supported in part by the Medical Department, United States Army and by the United States Public Health Service.

arteriovenous shunts. Other methods which are concerned with observation of changes in the blood flow in the skin have similar limitations.

Blumgart and Weiss in 1927 utilized radioactive substances in the study of the velocity of blood flow. Their method consisted of injecting an active deposit of radon into the antecubital vein of one arm and detecting its arrival in the opposite arm with a shielded cloud chamber. The radioactive substance used in these studies was radium "B" and its products in equilibrium. Although it rapidly decayed, with a half life of 26 minutes, the residuum persisting with disintegration was radium "D," which is also a radioactive isotope of lead, with a half life of 22 years. This isotope is deposited in bone and produces a prolonged radiation effect.

With the availability of other radioactive isotopes which are more satisfactory for use as tracers, additional methods for the study of the circulation have been developed. Smith and Quimby, Mufson (11, 12), and others have used sodium 24 as a tracer in evaluating circulatory diseases of the extremities. Sodium 24 possesses many characteristics which make it particularly suitable for such studies. It has a short half life (14.8 hours), and is not selectively absorbed by any tissues; it is relatively rapidly excreted, and is nontoxic to tissues. Its freedom from long-lived radioactive contaminants and its radiation spectrum make it harmless when used in small amounts. The quantity used in these studies resulted in a radiation to the body of considerably less than 1 roentgen. With the method employed, the radiation effect was even less significant. The emissions from the radioactive sodium consist of hard beta and gamma rays. The gamma rays are easily detected and recorded by electronic equipment placed outside the body.

ELECTRONIC APPARATUS

For this investigation, it was necessary to design an instrument which would permit accurate evaluation of radioactive tracers in studies of the circulation. Quantitative measurement of the radiation from sodium 24 in the tissues was made with an apparatus employing Geiger-Mueller tubes which operate an electromechanical system to record automatically and continuously the counts as detected by each tube (Fig. 1).

The Geiger-Mueller tube, its quenching circuit, and a cathode-follower amplifier are encased in a lead cylinder (Fig. 2). The thickness of lead eliminates about 50 per cent of the radiation from sodium 24 directed at the counter. Although this would not be satisfactory for taking counts in the presence of strong extraneous or scatter radiation, little difficulty was encountered in these investigations. The gamma radiation is admitted to the Geiger-Mueller tube through a window formed by removal of a portion of the lead wall; this aperture is covered by a thin aluminum shield. The detector is, therefore, close to the source of the radiation, resulting in a high rate of count from the area.

With this equipment, it is possible to operate four counting circuits simultaneously. These can be used to record counts from one, two, or three locations, a remaining circuit being used to record background and scatter radiation. The advantages of such a multiple system in circulatory investigations are evident, but would be offset by the confusion of taking data if an automatic recording system were not employed.

Pulses from a Geiger-Mueller tube are fed into a Lifschutz (9, 10) scaling circuit which accepts and "stores up" 32 counts before recycling. A special electronic circuit[1] translates the total number of counts accumulated by a scaler into a current which activates the pen of the mechanical recorder. Figure 3 shows the record that is made using this system. The "steps" in the figure indicate single counts, while each peak indicates every thirty-second count. At increasing rates where the individual counts disappear, interpolation of the number of counts is made possible by pre-adjustment of the translating circuit to give a deflection of one chart unit per count. At still higher rates, the inertia of the pen makes full swings impossible. At such rates individual counts are of no consequence. Each peak on the chart then indicates the reception of 32 counts. It can be seen that instantaneous changes in counting rates are indicated clearly by a definite change in the slope of the mounting curve. Thus the time at which radioactive material reaches a Geiger-Mueller detector can be determined to the second.

A method employing electronic integrating circuits driving graphic pen recorders was tested, but several weaknesses of this system proved it to be unsuitable for this study.

Four detectors containing Geiger-Mueller tubes are connected by flexible cables to a control panel on the wall of the examining room. From this point the cables extend through an electrical conduit to an adjoining room in which the recording circuits, amplifiers and power supplies are located. The injection

[1]Designed by R. H. Rohrer, Assistant Professor of Electrical Engineering, Emory University, and W. B. Miller, Jr., Electronics Consultant for the Department of Surgery. This circuit is described in an article "A Method of Automatically Recording Slow Random Counts," to be published.

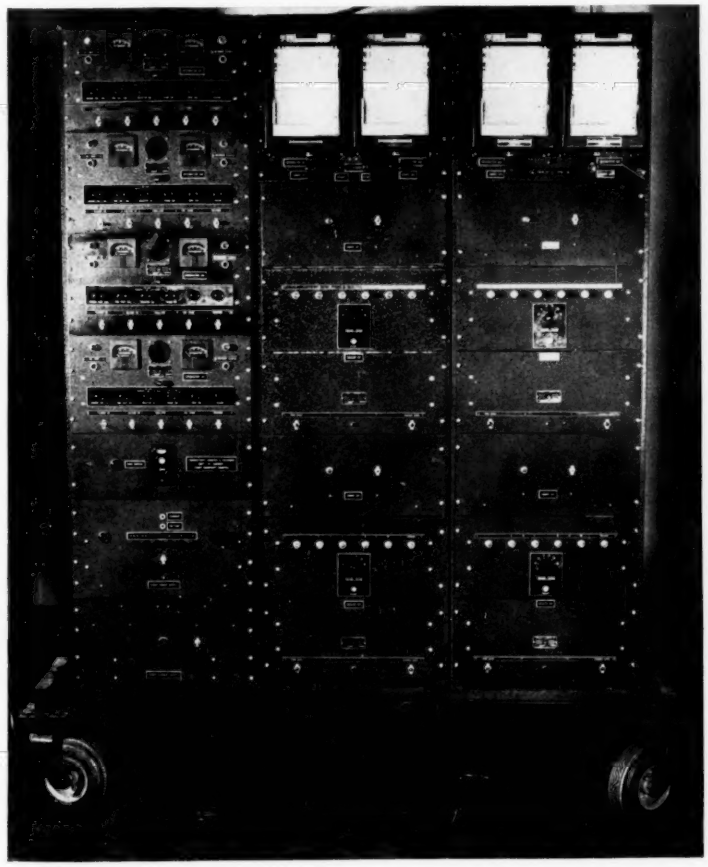

Fig. 1. Electromechanical apparatus used for automatically recording impulses received from the Geiger-Mueller tubes.

time of the sodium is indicated on the record by means of a foot switch in the examining room.

METHOD

Radioactive sodium carbonate is received from the pile at Oak Ridge, Tennessee. The mass obtained weighs 0.3 gram and is rated 35-110 milliroentgens of gamma radiation per hour at 24 inches from source of gamma radiation. This material is converted into sodium chloride by the addition of hydrochloric acid. Neutralization is effected by titration with sodium hydroxide. The resulting sodium chloride solution is evaporated to dryness and is redissolved in pyrogen-free distilled water, and sterilized by autoclave. Dilutions of the material are made depending upon the proposed method of utilization.

Two methods of study were employed: one, described by Smith and Quimby (12), involves the "build-up" of radioactive sodium in the tissues of the extremities following its intravenous injection in the arm. The second is a relative flow determination based on the rate of disappearance of radioactive sodium when injected intramuscularly, as suggested by Kety. It is obvious that the first method depends not only upon the flow of blood to

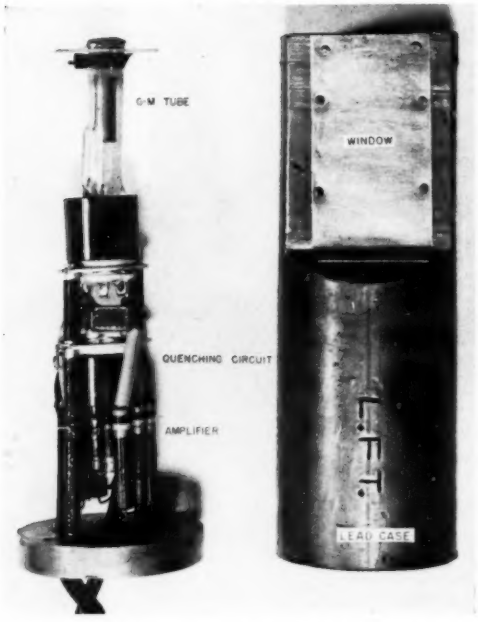

Fig. 2. The detector unit for reception of impulses from the radioactive sodium in the tissues.

the part but also upon the diffusion of the sodium chloride from the vessel into extravascular spaces. The second method is concerned with the mobilization of the sodium which has been injected into the muscle, and its removal from extravascular spaces by the effective circulating blood.

Method I. Intravenous injection of radioactive sodium. The patient was placed upon a tilt table in a room in which the temperature was constantly controlled at 78 degrees F. The legs were elevated at an angle of 35 degrees (Fig. 4). A detector was placed posterior to each gastrocnemius muscle and at the ball of each foot. Prior to administration of radioactive solution, the "background count" from cosmic rays and other extraneous radiation was recorded by the equipment.

Five cubic centimeters of the prepared solution, containing one to two hundred microcuries of radioactive sodium, was rapidly injected intravenously in the antecubital vein. The time and duration of injection was recorded. The syringe was removed from the room immediately following injection of the solution.

The circulation time to the leg was determined by the sudden, rapid increase in the rate of count (Fig. 3). The circulation time to the foot could not be accurately determined in all instances due to a gradual increase in concentration of sodium at this point. This increased concentration resulting from the establishment of an equilibrium of the isotope between the intravascular and extravascular spaces was recorded over a period of 30 to 45 minutes.

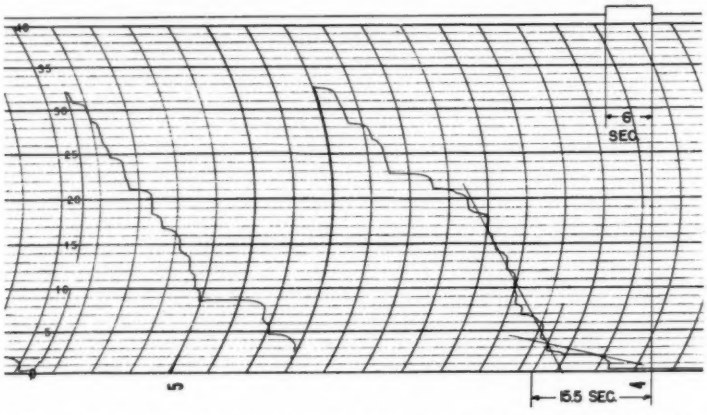

Fig. 3. Chart as recorded by the electronic apparatus. Single counts are indicated by the horizontal lines. Vertically curved lines represent intervals of 5 seconds. The marker indicates the time and duration of injection of the radioactive sodium intravenously.

Ninety individuals were studied by this method. Sixty of these had no demonstrable vascular disease. The curves plotted from their record formed an average pattern (Fig. 5). The persons observed, both male and female, varied markedly in build, muscular development, height, weight, age, obesity, and skeletal size. The amount of radioactive sodium injected was recorded. It was found that an unsatisfactory build-up curve resulted if less than 80 microcuries was injected. The variation between curves depended more upon the amount of sodium injected than upon any of the above factors. Therefore, in subsequent observations following the injection of drugs, or operation upon the vascular or sympathetic nervous systems, an identical amount of sodium was employed for comparative results.[1]

With this method of study, the random radiation from various portions of the body imposed an exceedingly difficult factor, and a marked increase in background count for each tube necessitated extensive shielding of the Geiger-Mueller detectors.

Method II. The injection of radioactive sodium into the muscle. Utilizing the same apparatus, studies were made following the injection of sodium directly into the gastrocnemius muscle. The solution was diluted so that each cubic centimeter contained 100 microcuries. The patient was placed either in a horizontal position or with the extremities

[1]Miss Mary H. Atkins was technician for this project.

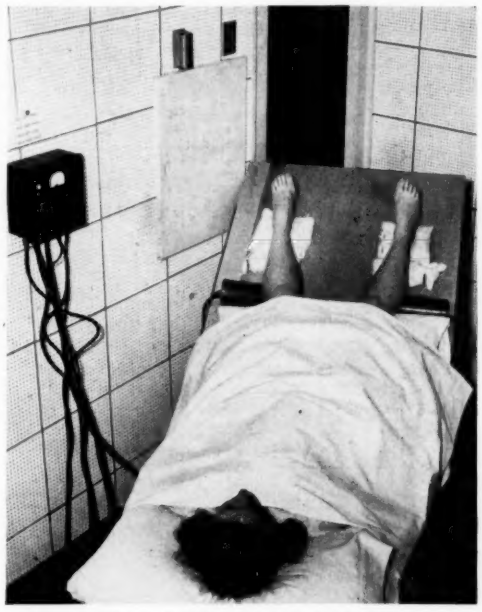

Fig. 4. Position of patient on tilt table with legs elevated. Detector units are placed at the site of injection of the radioactive sodium.

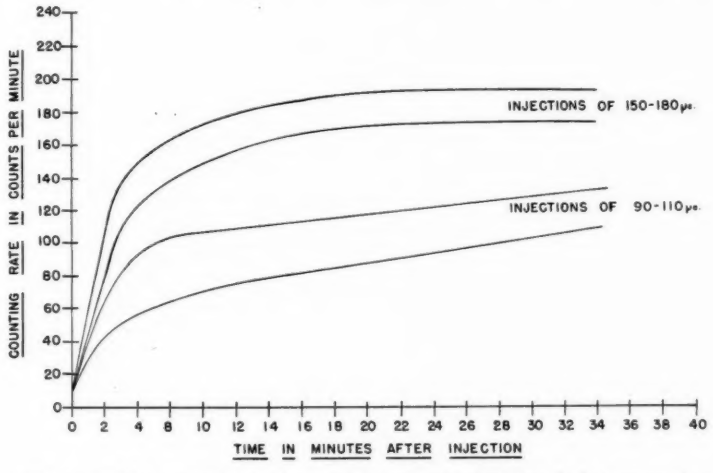

Fig. 5. Buildup curves in the tissues of the extremity following the intravenous injection of radioactive sodium chloride in normal individuals.

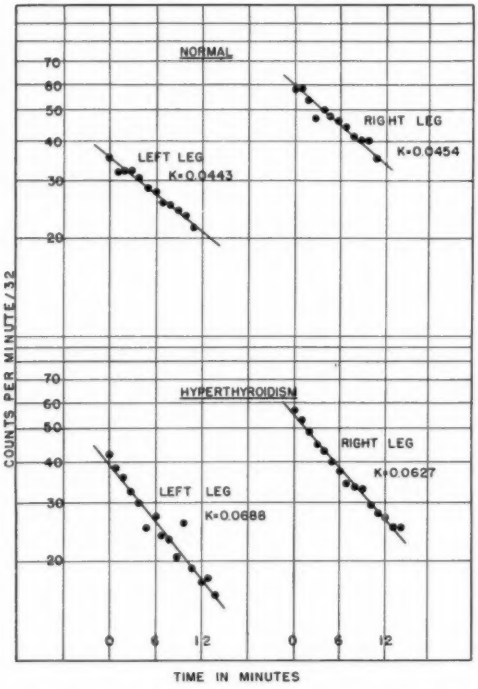

Fig. 6. Rate of disappearance of radioactive sodium when injected intramuscularly. Increase in rate of disappearance is indicated by a vertical inclination of the line.

elevated, and with a detector posterior to the superior portion of each gastrocnemius muscle. A third counter was placed at a short distance from the subject to record background radiation.

A volume of 0.2 cubic centimeter of this solution containing approximately 20 microcuries of sodium 24 was injected into each gastrocnemius muscle. In this study, the exact amount of radioactive material injected was of no significance, nor was it necessary to inject an identical amount into each calf muscle since the rate of disappearance as evidenced by the decrease in counting rate was the factor to be determined. The patient was constantly observed to insure the immobility of the extremities.

Following injection, the recording apparatus was operated for a period of 12 minutes prior to any alteration in the conditions of the experiment. After the initial or control run, various procedures could then be carried out, such as application of a tourniquet, the administration of drugs, the performance of sympathetic blocks, etc. After the procedure was performed the subject was returned to the original position and an additional 12 minute run was made to determine the effect of the therapy on the circulation of the extremities.

Since the amount of sodium injected into the muscle was small, no difficulty was encountered as a result of radiation from the opposite extremity, or from other parts of the body. Similarly, following the mobilization of the sodium into the vascular system, and its distribution throughout the body, the amount of sodium returning to the extremity through arterial channels was so low that background radiation was not increased.

It is apparent that this method of injecting the sodium directly into the muscle and recording its subsequent removal by the effective circulating blood permits an objective evaluation of the effective blood flow through the nutrient capillaries. While such a determination alone does not allow an exact estimation of blood flow per given muscle mass at this time, values are obtained which will permit accurate comparison.

DISCUSSION

In both of these methods, it was found desirable to elevate the extremity approximately 35 degrees above the horizontal. A stress factor was thus imposed which accentuated the degree of vascular insufficiency. Elevation in the normal individuals produced no changes in the disappearance rate. It has long been appreciated that pallor of the extremity on elevation is one of the simplest tests for vascular insufficiency. Buerger, Brooks, Homans, and others have emphasized that the rapidity with which color returns to the digits of the elevated extremity upon compression, indicates vascular sufficiency.

By the intravenous injection of radioactive sodium, the recording of its arrival time in the extremities and the subsequent build-up of the sodium in the extravascular spaces (method I), the circulation time to the extremities can be accurately determined.

The variations in the circulation time to the extremities found in normal individuals is so wide as to render these results valueless in the diagnosis of circulatory disorders. The arrival of the radioactive material at the part and the subsequent increase in concentration is dependent upon many uncontrollable factors. A measurement is not necessarily being made of the presence of the sodium in the larger arteries, but more accurately of that which has escaped into the extravascular fluids.

Through accurate standardization of the quantity of radioactive sodium administered for repeated determinations, comparative data can be obtained on the rate of increase in sodium concentration in the tissues of the extremities. This rate of increase is, to a degree, proportionate to the volume of blood flow to the extremity. An accurate determination of actual muscle blood flow as differentiated from flow to the various other tissues cannot be determined by this method, however. It also has a disadvantage in that it does not immediately reflect changes in the state of circulation in the extremity following the injection of drugs, therapeutic procedures, alterations in position of the extremity, or the utilization of mechanical devices which are devised to improve the blood flow.

With injection of radioactive sodium directly into the muscle, and the measurement of its rate of disappearance (method II), it is believed that a valuable method of determining the relative effective blood flow to the muscles has been obtained. It is apparent that the rapidity of removal of the sodium from the muscle depends upon the volume of blood flow.

When the results of this method are plotted on semilogarithmic paper with the number of counts per minute plotted on the ordinate and the time on the abscissa, a linear expression of the rate of disappearance of the sodium from the muscle is obtained (Fig. 6). The inclination of this line will remain unchanged while the conditions of this experiment are not altered. If the removal of sodium is prevented by the application of an arterial tourniquet above the site of injection, the line will become horizontal (Fig. 7). As the rate in which the sodium is removed from the muscle increases,

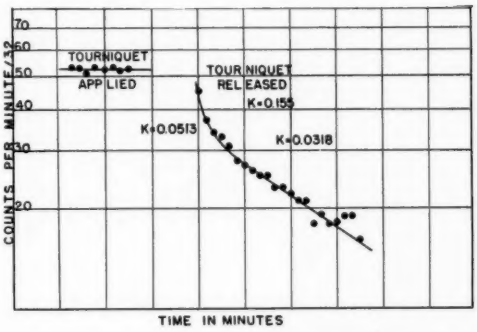

Fig. 7. Application of tourniquet prevents removal of radioactive sodium as represented by a horizontal line. Following release of tourniquet the resulting hyperemia removes the sodium more rapidly than normal with a more vertical line being obtained. Equilibrium is established as indicated.

the line will tend to become vertical. After removal of the tourniquet, hyperemia results in a more rapid removal of sodium, the normal rate being resumed only after disappearance of the period of hyperemia.

It is believed by Kety that a logarithmic expression of the slope of the line is valid for comparative studies. This expression, or "K" factor, is the natural logarithm of the slope of the line, and is determined by the equation:

$$K = \frac{\log C_1 - \log C_2}{.4343\ (T_2 - T_1)}$$

C_1 = counting rate at time T_1
C_2 = counting rate at time T_2

This latter method has been utilized in 115 individuals, both normal and with vascular disease. It has been used in normal individuals to evaluate the effect of certain drugs and other measures reputedly effective in enhancing the circulation in the extremities. Similarly it has been used in the evaluation of patients with vascular disease and their response to therapy. These observations are to be reported at a later date.

SUMMARY

1. Two methods for the use of radioactive sodium 24 in the investigation of circulatory physiology of the extremities are compared and discussed.

2. The apparatus is described in detail.

3. The results of one of the methods used in a series of normal individuals are evaluated. (The results of the other method are to be published later.)

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OBSERVATIONS ON PRODUCTION OF PERICARDIAL ADHESIONS AND LIGATION OF CORONARY ARTERIES

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CLINICAL and laboratory investigation directed toward surgical establishment of collateral circulation to myocardium was pioneered by Claude S. Beck (1–7). Three general methods have been used. O'Shaughnessy (16) brought an omental graft to the heart from the abdominal cavity through an incision in the diaphragm. Beck (5) used transplants of pectoral muscle. Several authors (10, 11, 13, 14, 16, 17) have produced adhesions between myocardium, pericardium, and epicardial fat believing that this procedure might offer a feasible method of approach.

It has been assumed that if anastomoses can be established between vessels of the pericardium and those of the myocardium, augmented circulation would occur that would partially alleviate anoxia of coronary insufficiency. Moritz and associates (14), using injections of colloidal lamp black, have shown that extracardiac anastomoses of branches of the coronary artery are increased by pericardial adhesions. O'Shaughnessy (18) also demonstrated that vascular connections will develop between vessels of myocardium and adherent or adjacent structures. They used histological and injection studies.

Irritating substances have been applied to the epicardium or injected into the pericardial sac during operation to produce adhesions (21). Materials usually employed (20, 23) have been inconsistently effective or have produced pleural effusion, foreign-body granulomatous reaction, or damage to the heart. Work by Heimberger indicates that certain detergents would produce adhesions with minimal side effects. Further studies have been undertaken to evaluate materials for production of adhesions and also function of the heart after adhesions. Rats, dogs, and one hog were used.

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EXPERIMENTS

For convenience experimental studies will be described in three groups: group I, formation of adhesions; group II, effect of adhesions; group III, effect of adhesions with coronary occlusion.

GROUP I. FORMATION OF ADHESIONS

Method. The materials to be tested were introduced into the pericardial sac of white rats through thoracotomy wounds. Operations were performed; positive pressure ether anesthesia and aseptic surgical technique were used. Six substances commonly employed by others and reported effective for production of pericardial adhesions were injected into the pericardial sac of 42 white rats. Also, various dilutions of 13 detergents were similarly injected into the pericardial sac of 94 rats. As a control, saline alone was injected into the pericardial sac of 10 rats. Also, a 5 per cent solution of monoethanolamine oleate was introduced into the pericardial sac of one hog by means of parasternal injections without thoracotomy.

Observations. Autopsies on the control series of rats sacrificed 14 to 25 days after operation and injection of normal saline revealed no adhesions. Substances usually employed by others and listed in Table I produced adhesions inconsistently. Three of them, talc, lycopodium, and asbestos, produced foreign body reaction (granulation); and one, talc, produced pleural effusion. Among the 13 detergents used (Table II) 9 produced damage to the heart and occasionally death, even in dilutions of 2.5 per cent. Three did not produce adhesions. Adhesions involving at least one-third of the pericardium were produced by 10 detergents used. Foreign body reaction was not produced by detergents and soaps, but some caused pericardial or pleural effusion. Ubiquitous adhesions with good vascularity were formed in the hog (Fig. 1).

Fig. 1. Subacute adhesions in hog's heart 35 days after injection of monoethanolamine into the pericardial sac. Above the thickened vascular pericardium are seen well developed vessels 15 to 60 micra in diameter, fibrosis, and a light infiltration of plasma cells and leucocytes.

Of the materials employed for injection, monoethanolamine oleate in a 5 per cent solution seemed to be the most efficacious and the least toxic. It was therefore employed to produce adhesions in the rats and dogs used for subsequent experiments.

GROUP II. EFFECT OF ADHESIONS

Possible effects of adhesions were studied by means of physical efficiency tests in rats, and venous pressures and electrocardiograms in dogs. Adhesions were produced in the rats used for these experiments by intrapericardial injection of 0.2 cubic centimeter quantities of monoethanolamine oleate and in the dog by injections of 5 cubic centimeters. Relative physical efficiency was tested in rats by forced swimming with 15 grain weights tied to the tail. All animals were sacrificed and examined post mortem after the period of tests for gross and microscopic study of the adhesions.

TABLE I.—PRODUCTION OF PERICARDIAL ADHESIONS WITH MISCELLANEOUS AGENTS

Sclerosing agent	No. of rats	Deaths due to agent	Adhesions	Granulation	Effusion
Talc	11	2	5	7	1
Lycopodium	13	2	4	5	0
Invert sugar	6	0	3	0	0
Glucose	4	0	0	0	0
Sucrose	4	0	0	0	0
Asbestos	4	0	3	3	0

TABLE II.—PRODUCTION OF PERICARDIAL ADHESIONS WITH SOAPS AND DETERGENTS

Sclerosing agent	No. of rats	Deaths due to agent	Adhesions	Granulation	Effusion
Triethanolamine lorol sulfonate	5	5	0	0	0
Sodium lorol sulfate	6	2	3	0	2
Sodium oleyl methyl tauride	5	1	2	0	1
Sodium psylliate	6	3	3	0	0
Drene	6	1	4	0	3
Sodium oleate	8	3	3	0	0
Tincture of green soap	2	2	0	0	0
Sodium stenol sulfate	5	0	3	0	0
Lorol dimethyl benzyl ammonium chloride	5	5	0	0	0
Sodium lauryl sulfonate	12	9	3	0	2
Sodium C12 alkyl benzene sulfonate	6	0	4	0	1
Sodium salt of coconut oil	5	0	2	0	0
Monoethanolamine oleate	23	0	22	0	0

Observations. Table III summarizes the effects of pericardial adhesions upon physical efficiency of rats, as determined by the swimming test. There was no significant change of swimming time after formation of adhesions. In Table IV observations on the effect of adhesions upon venous pressure of dogs are tabulated. There was little change either during the first month or up to 4 months. The electrocardiogram of dogs failed to show evidence of constrictive pericarditis, although in one instance 4 months following the formation of adhesions some decrease in amplitude was observed.

All animals were sacrificed after the test periods to determine whether evidences of altered circulation were present. None showed evidence of chronic passive congestion. The morphologic changes following pericardial injection of monoethanolamine oleate in the rat and the dog varied chronologically into three stages.

TABLE III.—EFFECT OF PERICARDIAL ADHESIONS UPON PHYSICAL EFFICIENCY OF RATS

Rat	Swimming time prior to injection—seconds	Swimming time after adhesion formation—seconds
1	85	95
2	100	110
3	70	85
4	110	90
5	105	95
6	103	95
7	85	90
8	115	108
9	95	110
10	80	78
Average	94.8	95.6

1. Acute. The first stage lasting 7 to 10 days was characterized by presence of fibrin, polymorphonuclear leucocytes, and round cells on the epicardial and pericardial surfaces. Although little effusion was observed in rats, approximately 10 to 15 cubic centimeters of fluid was often found in the pericardial cavity of dogs. Evidence of fibrosis or of vessel proliferation was not found during this stage.

2. Subacute. The subacute phase lasted about 10 to 24 days in the dog and rat and was present at about 35 days in the hog. It was characterized by gradual disappearance of fibrin and development of light fibrous connective tissue joining the two serous surfaces (Fig. 2). Most interesting and important was the development of communicating blood vessels, which appeared at this time. These vessels were well formed, dilated capillaries, for the most part, with lumina about 12 to 60 micra in diameter and full of blood. Some of the vessels had a thin outer coating representing adventitia and possibly muscularis. Most, however, were smaller.

3. Chronic. In the third, the chronic, stage, little was seen except a moderately thickened, adherent, fibrotic pericardium with little cellularity or vascularization.

GROUP III. EFFECT OF ADHESIONS AND CORONARY OCCLUSION

Methods. Ligation of the anterior descending branch of the left coronary artery was performed through a thoracotomy incision using

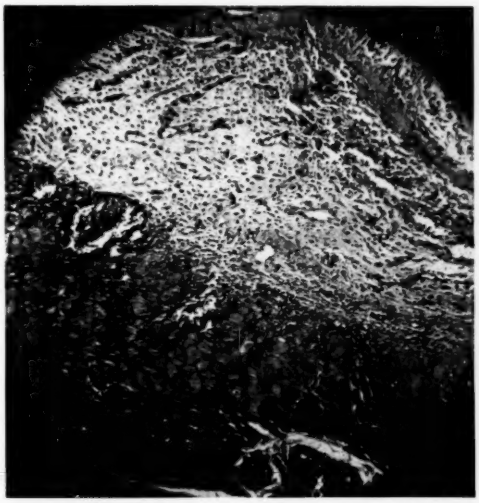

Fig. 2. Rat heart with subacute vascular adhesions. Above the intact myocardium is seen the vascular thickened epicardium-pericardium adhesions with well formed capillaries. The subacute inflammatory process seen on the outer surface of the pericardium is the result of leakage that occurred in many of these rats after injection.

No. 6–0 silk in the rat and No. 3–0 silk in the dog. Swimming time in the rat and electrocardiograms and venous pressures in the dogs were employed to test the effects of ligation alone and of ligation and adhesions. The effect of coronary occlusion produced prior to or up to 1 month following formation of pericardial adhesions was studied in rats. A series of dogs

TABLE IV.—EFFECT OF ADHESIONS ON VENOUS PRESSURE

Preoperative (cm. H_2O)	Less than 1 month postoperative (cm. H_2O)	More than 1 month postoperative (cm. H_2O)
24		27
16		11
21		26
26		29
25	18	14
24	26	
12	23	
16	19	
18	22	
19	26	
Average 20.1	22.3	21.4

Fig. 3. Myocardial infarction in the rat heart 1 month after ligation of the left coronary artery.

was also studied in which coronary ligation was performed alone or following the formation of pericardial adhesions.

Observations. The extent of decrease of swimming time following coronary ligation is illustrated in Table V. It is evident that a significant decrease in relative physical efficiency occurred after ligation. Infarcts developed in the myocardium of the left ventricle of each rat (Fig. 3).

In a series of 8 rats, ligation of the left coronary artery was followed within a few days by injection of the pericardial sac and production of adhesions. Swimming times were obtained 1 month later; results are summarized in Table VI. In 5 rats adhesions were produced 1 month after coronary ligation. Swimming times were obtained before ligation, 1 month later before injection to produce adhesions and 1 month after adhesions (Table VII).

The venous pressures of 2 dogs to be treated by ligation of their coronary arteries averaged 16.7 centimeters of water before operation. One and 2 months after ligation, their pressures averaged 15.0 centimeters of water. Ligation of the left coronary artery was performed in 4 dogs 10 to 24 days after injection of the pericardial sac during the stage described above as subacute or having vascular

TABLE V.—A COMPARISON OF SWIMMING TIMES BEFORE AND AFTER CORONARY LIGATION

Rat	Prior to ligation—seconds	One month postoperative—seconds
*1	106	45
*2	125	90
*3	120	94
*4	90	50
5	110	90
6	80	80
7	95	85
8	53	60
9	95	75
10	105	87
11	85	77
Average	96.7	75.7

*The four rats having large infarcts.

TABLE VI.—EFFECT OF PERICARDIAL ADHESIONS PRODUCED WITHIN A FEW DAYS AFTER CORONARY LIGATION

Rat	Swimming time prior to ligation—seconds	Swimming time 1 month after ligation and production of adhesions—seconds
1	105	95
2	98	105
3	115	93
4	90	50
5	115	58
6	108	70
7	95	100
8	102	88
Average	103.5	82.4

TABLE VII.—EFFECT OF PERICARDIAL ADHESIONS PRODUCED ONE MONTH AFTER CORONARY LIGATION

Rat	Swimming time prior to ligation—seconds	Swimming time 1 month after ligation—seconds	Swimming time 1 month after production of adhesions and 2 months after ligation—seconds
1	63	35	45
2	117	80	70
3	108	40	60
4	89	40	54
5	65	50	56
Average	88	49	57

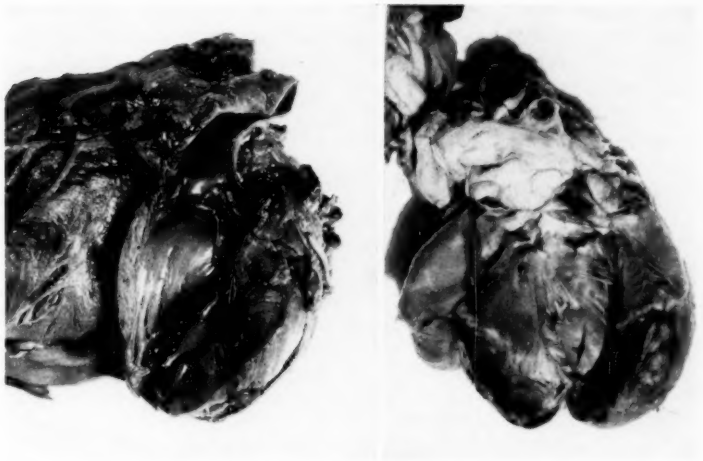

Fig. 4. Myocardial infarction in the dog heart produced, a, left, in the presence of the early subacute stage of pericardial adhesions, and, b, in the absence of pericardial adhesions.

adhesions. This effected a change of venous pressure from an average of 16.7 centimeters before ligation to 24.5 centimeters during the first several days afterward.

Electrocardiograms obtained before and after coronary artery ligation in each of the above two groups of experiments revealed changes of pattern characteristic of anterior infarction.

Autopsy revealed large infarcts in the wall of the left ventricle of each of the above dogs. Typical infarcts are presented in Figure 4. The microscopic appearance of these infarctions and of adhesions produced 4 weeks or more before autopsy are presented by a representative section (Fig. 5).

OBSERVATIONS

Experiments have indicated that monoethanolamine oleate in 5 per cent solution when injected into the pericardial sac of the rat, dog, or hog produces good adhesions without undesirable side effects. Adhesions are fibrinous for 7 to 10 days, then fibrous and vascular another 10 to 35 days, and subsequently fibrous and avascular.

Adhesions themselves produce no change in relative physical efficiency of rats as determined by swimming times or by venous pressures or electrocardiograms of dogs during 1 to 4 months of observation. Autopsies revealed no evidence of constrictive pericarditis or of passive congestion.

Ligation of the anterior descending branch of the left coronary artery in rats produced

Fig. 5. Avascular fibrotic pericardium characteristic of the chronic stage of pericarditis in the dog. Scarring of the myocardium, evidence of an old infarction, is seen above. At 4 o'clock is a bit of suture material.

infarction of the muscle of the heart wall with reduction of relative physical efficiency as evidenced by decreased swimming times. Injection of the pericardial sac a few days after ligation did not change this decrease of swimming time. Adhesions produced a month or more after coronary ligation did not produce significant increase of swimming time. The slight increase shown in column 3 of Table VII could be explained by gradual improvement in function of the heart after the ligation and would probably occur even though the adhesions were not present.

Ligation of the coronary artery of dogs during the subacute or "vascular" stage of adhesions was followed by typical infarction and by some heart failure as judged by increase of venous pressure.

Pericardial adhesions evidently neither alleviate the diminished function following coronary ligation nor hasten recovery. Neither do they effect a significant reduction in the size of myocardial infarcts. There were, however, fewer changes in the postligation electrocardiograms of those dogs having pericardial adhesions before ligation.

CONCLUSIONS

1. These studies have not yielded evidence to support treatment of patients with myocardial ischemia by production of pericardial sac adhesions.

2. Blood vessels that appear 7 to 10 days after production of adhesions are replaced within a month by avascular scar tissue.

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PRINCIPLES OLD AND NEW OF RESECTION OF THE COLON FOR CARCINOMA

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SINCE the first successful resection and anastomosis of the bowel for carcinoma by Reybord in 1832, the problem of removal of a segment of bowel and restitution of continuity has been a continuing challenge to all abdominal surgeons. It shares with all other surgical procedures the improvement in results following the many advances in the care of patients that have occurred in recent years, tending, I believe, more nearly to standardize the surgical treatment of cancer of the colon than has been possible before.

I am intentionally avoiding a statistical approach to this problem but rather have chosen to review the more important contributions, through the application of which the writer has developed his present concept of the management of these cases. I am intentionally limiting this discussion to resection of the colon for cancer because this involves the dual problem of proper treatment of the cancer and the technical aspect of resection and anastomosis. I am excluding the lower segment of the large bowel, which has been treated by combined abdominoperineal excision or by anterior excision with a permanent colostomy.

LYMPHATIC SPREAD

As I see segments of bowel resected for carcinoma which have been brought to the laboratory, I cannot but conclude that in many instances the surgeon has been so concerned with the technical aspect of re-establishing continuity that the primary problem of curing the patient of his cancer has been neglected.

The primary objective of an operation for cancer is complete eradication of the disease. If complete resection is to be accomplished, it must be foremost in the surgeon's mind, and the operation planned must have this as the primary objective. To plan an adequate resection presupposes an understanding of the vascular supply to, and lymphatic drainage from, the colon with particular reference to the amount of tissue which is to be removed if the patient is to have the optimum opportunity of cure.

In 1909, Jamieson and Dobson, after careful study of prepared specimens, presented an excellent description of lymph drainage from the various segments of the colon. They called attention to the line of first defense, the so-called paracolic glands, located along the arcades on either side of the lesion, and of the concentration of the drainage from these into the intermediate glands, situated between the arcades and the origins of the colic and sigmoidal vessels, all of which are removed in an adequate surgical excision (Fig. 1). On a basis of this study, they suggested the amount of tissue which should be removed in order to offer the proper protection from lesions in the several segments of the bowel (Figs. 2a, b, and c).

The recent work of Gilchrist and David on the lymphatics of the rectum, and of Coller, Kay, and MacIntyre on the colon would seem to have definitely established certain additional facts: (1) By the time the patient is operated upon, more than half of the lesions (rectum 69 per cent, colon 60.8 per cent) will have metastasized to the regional nodes. (2) Metastases may occur without gross changes in the nodes, be unnoticed by the surgeon and demonstrated by the pathologist only after the application of special techniques. (3) While the normal flow of lymph coincides with the direction of venous return, an alteration of flow will result and metastases may occur in a retrograde direction if a given lymph channel is blocked. (4) The size of the local lesion is no criterion as to the presence or absence of nodal metastases.

The practical application of these studies to amount of tissue to be removed at operation will be discussed later.

Arthur Dean Bevan Lecture, Chicago Surgical Society, October 3, 1947.

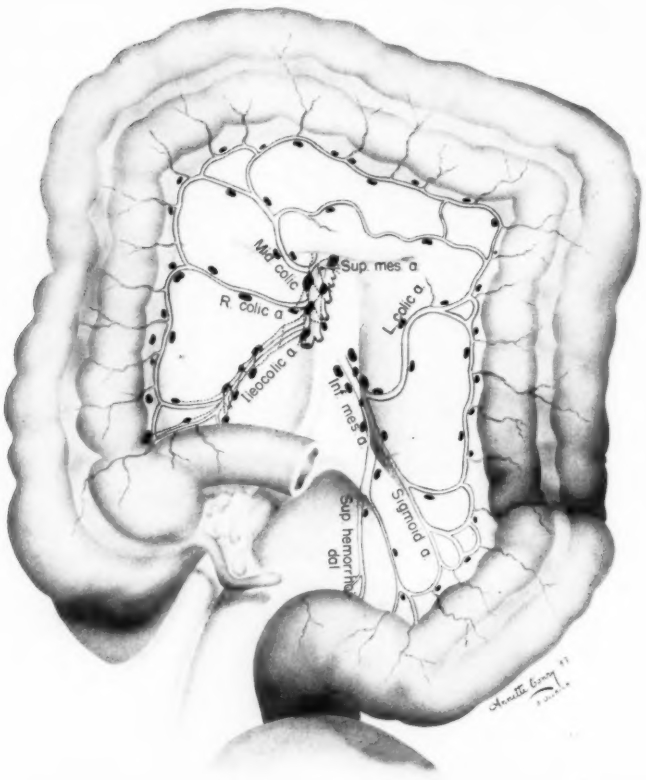

Fig. 1. Showing arterial supply and distribution of more important lymph nodes. The epicolic nodes on the wall of the bowel are considered of lesser importance and are not shown.

DEVELOPMENT OF TECHNIQUE OF RESECTION AND ANASTOMOSIS

The observations by Lanfrank in 1396 and Travers in 1812 that healing of the intestines to the parietal peritoneum and to each other came through the agglutination of the serosal surfaces, followed in 1826 by Lembert's description of a method of suture which would hold in apposition the serosal surfaces of two segments of bowel to be united, represent the earliest contributions to intestinal resection. Little of significance followed until 1892, when two contributions of great importance appeared in the literature—the introduction of the "anastomosis button" by John B. Murphy and the description by Oscar Bloch, of an entirely new approach to the problem by the extra-abdominal removal of a segment of bowel. Murphy, in describing his "anastomosis button" said, "If means can be devised—1st, to hold the surfaces in contact; 2nd, while in contact, to produce a speedy and permanent adhesion of the surfaces; 3d, to keep an opening sufficiently large for the free passage of intestinal contents; 4th, to produce as a result a cicatrix that will not contract to any great extent and by the contraction produce complete or partial obstruction—we will have overcome the great barriers remaining between us and ideal success in intestinal surgery."

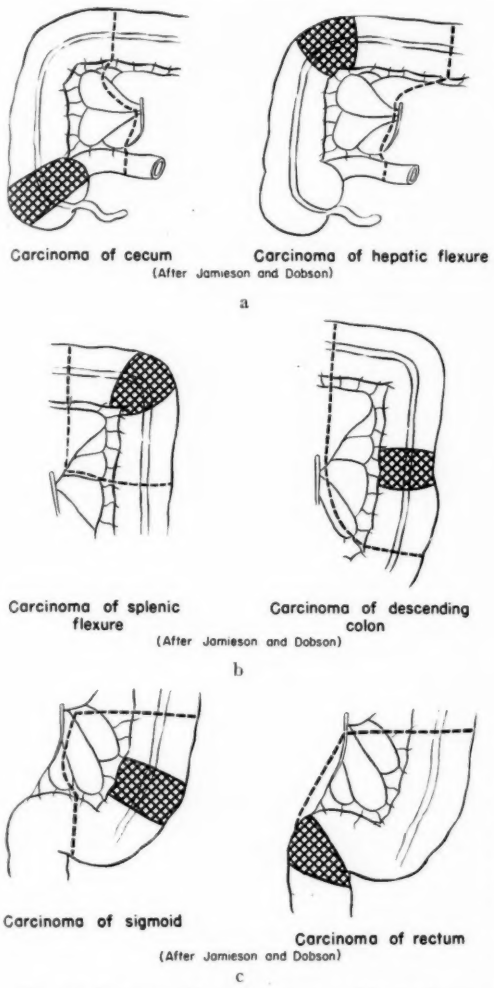

Fig. 2. a, Segments of bowel to be removed for carcinoma of cecum, left, and hepatic flexure, right, as suggested by Jamieson and Dobson. b, Segments of bowel to be removed for carcinoma of splenic flexure, left, and descending colon, right, as suggested by Jamieson and Dobson. c, Segments of bowel to be removed for carcinoma of sigmoid, left, and rectosigmoid, right, as suggested by Jamieson and Dobson.

In that same year Bloch, in Norway, discouraged by the high mortality following primary resection of the bowel for cancer (he gives reports from various clinics showing mortality rates of from 47 to 59 per cent), conceived an operation whereby peritonitis

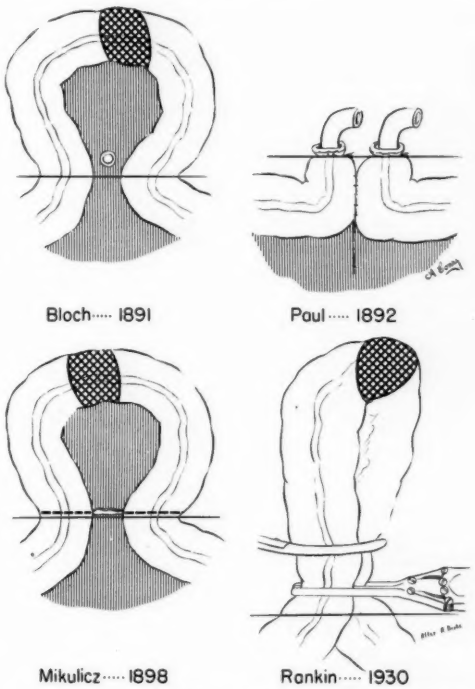

Fig. 3. Schematic representation of operations described by Bloch, Paul, Mikulicz, and Rankin.

could be avoided by doing the actual resection of the bowel outside of the abdominal cavity. A short (6 cm.) incision was made just above and parallel to the inguinal ligament, a long loop of sigmoid with the carcinoma at its apex was withdrawn through this wound and anchored to the wound at either end, an opening was made in the mesentery well away from the growth through a relatively avascular area where there were no enlarged nodes, and a glass spatula put through this (Fig. 3). Two sutures were placed on either side of the bowel approximating the afferent and efferent loops. A rubber tube was placed in the proximal segment for relief of the obstruction. One month later, the bowel and mesentery were divided and an attempt was made to do an extra-abdominal anastomosis between the two ends. This anastomosis failed. The patient was discharged 6 weeks later, remained well, gained in health, and returned after 2½ months

(about 5½ months following the original operation). At this time an end-to-end closure was done in the wound. The anastomosed segment of bowel was then freed and replaced in the peritoneal cavity. The patient had a relatively uneventful convalescence, was discharged, and died at a later time of metastatic cancer of the liver.

Three years later, Mr. F. T. Paul, surgeon to the Liverpool Infirmary, apparently unaware of the work of Bloch, describes 7 cases from which he evolved a logical, finished concept of the management of cancer of the large bowel. The presentation of these cases is an excellent example of orderly thinking and warrants brief comment. His first case—a woman of 49 with obstruction and vomiting due to cancer of the sigmoid, was operated upon, a very favorable growth removed, and a difficult anastomosis carried out "by invagination on the decalcified bone." Death the night of operation was thought to be due to a long, difficult operation as well as to the slight leakage which was found at postmortem. The next case—a woman of 47, entered with complete obstruction due to a large carcinoma of the sigmoid. A right lumbar colostomy was done to relieve the obstruction. Ten days later, the growth was resected. The operation was difficult and the patient's condition too poor to warrant suture of the ends of the bowel so that they were brought out through the wound as had been done on previous occasions by a number of other surgeons. This patient died at the end of 36 hours, and Paul makes the following note: "I consider that the loss of this case was due chiefly to a want of appreciation of the profound and prolonged effect of a serious attack of intestinal obstruction, partly to the absence of sufficient technical skill." His third case—a 47 year old woman with a cancer of the cecum, also had a resection and what he considered a very satisfactory anastomosis by the "bone-tube method." This patient also died of peritonitis, which he thought might have been due to restriction of too much blood supply. And in discussing this death, he makes the following note: "The sloughing of the cut end of the colon would probably have taken place with any mode of approximation; but had it been outside instead of inside the peritoneal cavity, the small area of gangrene would have done no harm." His fourth case—a woman of 60, ill with acute obstruction of 9 days' duration, was operated upon through a left inguinal incision. The sigmoid with the obstructing lesion was withdrawn through the wound, the bowel was clamped, a portion of the bowel containing the growth was excised, and a glass intestinal drainage tube was sutured into each end of the bowel. The dressing was then applied and the proximal end of bowel permitted to drain into a basin. This patient made an uneventful convalescence and died 2 years later, at which time postmortem examination failed to reveal any evidence of recurrent disease. This operation was done in May, 1892. Mr. Paul noted, "One might conclude that when the excision was not too extensive and the ends of the bowel brought out correctly, it might be undertaken with comparatively little danger to life." Case 5—a patient of 38, without marked obstruction, was operated upon for a carcinoma of the descending colon. The bowel was freed from the splenic to the sigmoidal flexure, the mesentery carefully tied, ligated and divided, the bowels brought out through the wound, and the glass tubes inserted. This patient, too, made an uneventful convalescence. Paul was not content, however, to permit this patient to go through life with a permanent colostomy and 5 weeks after the original operation an attempt at closure of the colostomy was carried out. The patient died of peritonitis 4 days later. Paul, in reviewing this case, expresses his disappointment at having evolved a method of resecting a tumor safely only to have the patient die in attempting to avoid a permanent colostomy. He then makes the following interesting statement:

"There remained, however, to be tried the old plan of restoring continuity by Dupuytren's enterotome, to which very little risk is attached. If such a method could be perfectly successful when the spur was accidentally formed by nature, how much more ought it to be so when a spur was deliberately constructed with the object of being subsequently safely removed? I have, therefore, brought out and determined to put in practice the following method of operating in the next case: First, excise the strictured portion of bowel as in the last 2 cases; then suture together the cut edges of the mesentery and the adjacent sides of the two ends of the colon, in

such a manner that they would adhere together for about 3 inches, in the position of two barrels of a double-barreled gun. If this succeeded, the spur might be demolished without the slightest risk of peritonitis, and to such an extent as to insure a free passage and easy closing of the artificial anus" (Fig. 3).

His next case, done according to this concept, had the growth removed and the colostomy successfully closed. In the final case reported the patient died following operation before the anastomosis was carried out. Death was due to uremia, as proved by autopsy. There was no peritonitis, and the two parallel limbs of bowel which he had sutured were well healed. It is of interest that Paul's final conclusions formed on a basis of these experiences were:

"When the patient is in good condition, the abdomen not distended, the tumor small, and the proximal end of the bowel not greatly hypertrophied, I advise immediate approximation by Murphy's button method. But when the opposite of these conditions prevails, I strongly urge that the ends of the bowel should be brought out in the manner explained and illustrated; and I feel sure, though I have been unfortunate in the sort of cases I have had to deal with, that this method of bringing out the ends is much safer than any other plan of immediate approximation, all statistics notwithstanding."

It need only be added that Mikulicz in 1903, referring to Bloch's work, but making no reference to that of Paul, described and strongly advocated the exteriorization type of operation. His plan was to mobilize the bowel, divide the mesentery to include removal of regional nodes, bring the loop through the wound, close the abdominal wall, apply a dressing, and remove the growth in 12 to 48 hours or immediately (Fig. 3). A tube was placed in the proximal segment. He did much to popularize this procedure and to bring it before the English-speaking world, particularly the surgeons of this country, through his writing and particularly through its inclusion in a system of surgery published in this country in 1904 (2).

This procedure was brought to its highest state of perfection by Rankin in his article, "Obstructive Resection," published in 1930. Without question, the development and utilization of the principles involved in these procedures represent the greatest single contribution to the safety of resection of the large bowel that has been made.

The early frequent wound recurrences due to inadequate operation, which often followed the exteriorization procedures and the long period of disability, stimulated surgeons to continue their quest for safer methods of primary anastomosis. In the gradual evolution of this method, certain serious hazards were recognized. Of greatest significance was the rôle of obstruction so well expressed by Paul in his article and stressed so much by the many writers in this country. It is impossible to know to whom credit should go for insistence upon proper attention to the obstructed bowel and particularly to the development of the importance of relief of obstruction through proximal decompression. Again it is of interest that Paul in 1891 did a right lumbar colostomy as a preliminary procedure in a patient with acute obstruction, upon whom a diagnosis of cancer of the left colon had been made (Case 2 above). Jones, Cheever, Rankin, Whipple (19), Bevan, and many others advocated and repeatedly stressed the importance of proximal decompression until it was accepted by most surgeons of experience as an essential part of resection with primary anastomosis. Proximal decompression for resection of the colon probably reached its highest state of development with the use of the Miller-Abbott tube as described by Whipple (20).

In the earlier days of direct anastomosis, outstanding contributions were made by the development of simple and safe methods whereby anastomosis could be carried out with closed bowel, thus avoiding the dangers of contamination from the open ends of the transected intestine. Of the many methods described, the writer has preferred that of Parker and Kerr, whose anastomosis utilized the principle of a basting stitch rather than instruments. It has proved to be simple, useful, and safe.

Stone and McLanahan in 1939, stressing the importance of the closed anastomosis, recognized the diminishing need for proximal decompression and may well have ushered in the modern era of safe intestinal anastomosis without its use except in selected cases with obstruction.

TABLE I.—TYPES OF OPERATION AND MORTALITY RATES—1932–1941

	Number	Deaths	Mortality rate %
Anastomosis with proximal decompression	40	6	15
Anastomosis without proximal decompression	2	0	0
Obstructive resection	13	0	0
Right colectomy, one stage	15	3	20
Right colectomy, two stages	20	1	5
Totals	90	10	11

PRINCIPLES GOVERNING SAFE ANASTOMOSIS

Along with the development of safer methods of suture and the acceptance of proximal decompression, certain basic principles were stressed as essential or of great importance in the completion of a safe and proper operation. Thus, Bevan in 1920, was governed by three basic principles: (1) proper selection of incision, (2) free mobilization of the bowel in relation to the growth, and (3) the use of a lateral rather than end-to-end anastomosis. The writer, during his long association with D. F. Jones, constantly heard stressed the importance of three fundamental principles in any intestinal anastomosis: (1) adequate blood supply, (2) avoidance of excessive intraintestinal pressure through proximal decompression, (3) avoidance of any tension at the suture line.

Improved methods of anesthesia and a better understanding of the many aspects of patient care have resulted in such improvement in results following all major surgical procedures that we may now revise our thinking in relation to intestinal resection, bringing together experiences of the past with the developments of the present.

We might then present what we consider to be the essential basic principles for resection of the colon for cancer:

1. Proper preparation of the patient for operation.
2. Optimum exposure of the segment of colon to be excised.
3. Adequate mobilization of bowel.
4. Adequate cancer operation.
5. Free blood supply to both segments.
6. Avoidance of tension on suture line.
7. Proximal complete colostomy, if adequacy of suture line or blood supply is in doubt.

Preparation of the patient. The name of Rankin more than any other one surgeon is associated with careful and adequate preoperative preparation of any patient who is to be operated upon for cancer of the large bowel. Only in recent years, however, has the real importance of this become apparent to all surgeons. We customarily require from 5 to 10 days, or more, of hospital care in preparation of a patient for resection. Just how long proper preparation will take is dependent upon a number of factors relating to the degree of obstruction and the general condition of the patient. Rather than state the time involved, one might better state the objectives to be obtained. Unless repeated hemorrhage or some other complication prevents, every effort should be made to have the patient go to operation with a deflated, empty, well prepared bowel. He should be well nourished, with a serum-protein level and hemoglobin within normal limits, and have had an adequate or excess vitamin intake. In the absence of more than a mild degree of obstruction, this is accomplished by the use of an active cathartic on the afternoon of admission (our preference is for castor oil but any active cathartic is satisfactory), sulfasuxidine or sulfathalidine (the former if there is any degree of obstruction) for a minimum of 5 days, a low residue diet containing from 100 to 125 grams of protein daily, the use of some potent polyvitamin in excess of the normal needs, and blood transfusions to bring the hemoglobin to within normal limits. The use of the scout film to determine the amount of material in the bowel proximal to the lesion is very helpful. It has been our experience that patients with mild to moderate obstruction will empty out their bowels in a completely satisfactory way following the use of sulfasuxidine and small divided doses of a saline cathartic if sufficient time is allowed. In those patients who cannot be otherwise adequately prepared, particularly in those patients with complete obstruction, some form of proximal decompression is necessary. In the completely and acutely obstructed patients, it is our policy to do a cecostomy under novocaine, suturing a half-inch rubber tube into the distended cecum by several infolding sutures. If after release of the acute

obstruction, the bowel cannot be satisfactorily prepared either through spontaneous restoration of bowel activity or the use of irrigations through the cecostomy tube with the Miller-Abbott tube as suggested by Millett, a transverse colostomy is done. This is placed to the right of midline if the splenic flexure is to be mobilized; otherwise, in or to the left of midline. As will be noted, proximal surgical decompression has been used in only a small proportion of cases in the recent years (Table II).

We now use the Miller-Abbott tube in preparation for operation only on certain indications. If the patient has a large, full abdomen or a tendency to slight distention, the Miller-Abbott tube is started 48 hours before time of operation in the hope that it may be well into the lower small bowel at the time of resection. This not only provides proximal decompression, but the fluting of the bowel on the tube markedly increases the freedom with which the operative procedure can be carried out. In those cases in which the Miller-Abbott tube is not to be used, the Levin tube is inserted into the stomach the afternoon before operation and placed on suction in order to eliminate all swallowed air from the intestinal tract for a period of 12 to 18 hours before the time of operation. This insures a deflated stomach and does lessen the amount of gas that will be found in the small bowel.

Incision. Experience with various types of incisions in patients who have been operated upon has convinced me that the only important consideration in the selection of an incision is the amount of exposure which is given throughout all aspects of the proposed operation. The incision most frequently used for resections in the right half and the left half of the colon is a long right or left rectus muscle splitting incision. This is particularly useful on the left, where, as will be later shown, most resections involve mobilization of the splenic flexure above and an anastomosis which may frequently involve working with the distal sigmoid in the lower abdomen. The transverse incision gives excellent exposure for a resection and anastomosis of the transverse colon. In general, an incision placed parallel to the long axis of the bowel to be resected will afford optimum exposure of that particular segment.

TABLE II.—TYPES OF OPERATION AND MORTALITY RATES—1942–1947

	Number	Deaths	Mortality rate %
Anastomosis with proximal decompression	12	2	16.6
Anastomosis without proximal decompression	67	4	5.9
Obstructive resection	1	0	0.0
Right colectomy, one stage	43	0	0.0
Right colectomy, two stages	6	1	16.6
Total operations	129	7	5.4
Total resections with primary anastomosis	110	4	3.6

Adequate mobilization of bowel. We have become increasingly convinced that Bevan's insistence upon adequate mobilization of the bowel is one of the most important factors in resection of the left colon. Except for the occasional lesion which we find at the apex of a long loop of sigmoid or for the lesion in the lower sigmoid, it is our policy to mobilize the splenic flexure and a portion of the transverse colon in all cases. If the incision is properly placed and of sufficient length, if the dissection is started in the region of the sigmoid or descending colon and carried up around the splenic flexure, mobilization of the splenic flexure (unless there is a large tumor in that area) is not difficult nor is it hazardous. Not only is this necessary in order to do an adequate operation for many of the lesions in the left colon, but the increased mobility of the upper and lower segments of bowel makes it possible to bring the ends to be joined into the wound outside of the abdomen, insuring freedom of action and complete absence of tension on the line of sutures. It is our feeling that this procedure has contributed more to the safety and to the ease of left colectomy than has any other single maneuver.

Adequate cancer operation. In Figures 4 and 5 are shown the segments of bowel which we believe should be removed for cancers located in the various segments of the colon in order to give the patient the best chance of permanent cure. It is recognized that this is a schematic presentation and that abnormalities in blood supply or physical set-up will frequently make impossible the carrying out of what we believe to be the theoretically correct procedure. It

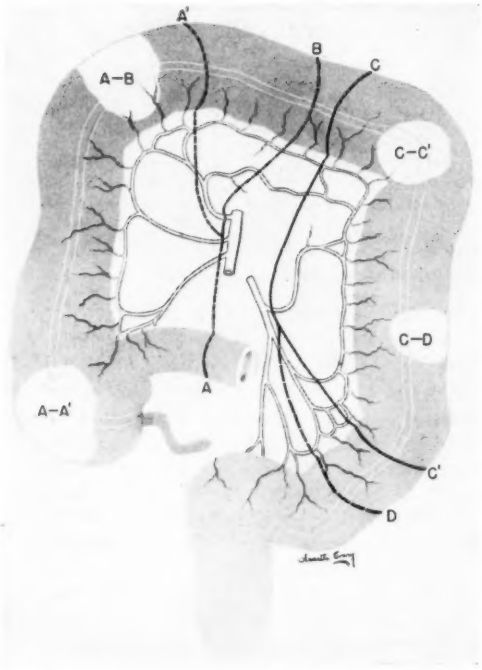

Fig. 4. Schematic representation of segments of bowel and mesentery which should be removed for carcinoma of cecum, *A–A'*, hepatic flexure, *A–B*, splenic flexure, *C–C'*, and descending colon, *C–D*.

is, nevertheless, surprising how frequently one can approach the ideal if that is the major objective of the surgeon, particularly if the concept of complete mobilization is accepted. A very free anastomosis between the vessels and presumably also the lymphatics above the level supplied by the superior hemorrhoidal artery makes it desirable, at least on the theoretical basis, to remove a long segment of normal bowel and mesentery below the margin of the growth as well as above. We prefer a minimim of 3 inches of normal bowel and accompanying arcade of vessels and lymphatics on either side of the lesion with inclusion of the lymphatic drainage to as high a level on the primary branches of the superior or inferior mesenteric arteries as local conditions will permit.

Blood supply. There can be no question but that the importance which Jones placed upon adequate blood supply cannot be overestimated. Primary suture in the absence of a completely adequate blood supply will result in leakage; and unless there is proximal diversion of the fecal stream, severe sepsis or death may occur. Normally and probably in many instances the free collateral exchange between the various branches of superior and inferior mesenteric arteries will insure adequate supply over a long segment of bowel even if primary branches are divided so long as the arches are left intact. Nevertheless, surgeons and students of the blood supply to the large bowel are aware of the many anomalies which exist, and it is our judgment that assurance of adequate blood supply is not to be based upon a knowledge of what the anatomy should be but upon an actual visualization of pulsating or bleeding vessels at the margins of divided bowel to be anastomosed. If we cannot see actual pulsating vessels so situated as to insure blood supply to the cut end, it is our policy to transect intentionally a small vessel before a clamp is applied in order to visualize free arterial bleeding. Only under these conditions can one be assured that anastomosis can be safely carried out.

Avoidance of tension. Too often, surgeons forget that sutures merely represent a method of holding in approximation the segments of bowel to be joined. They are not a means of bringing together two segments under tension and temporarily keeping them in place. Any two ends of bowel which are to be united must lie in easy approximation and be completely free from tension.

Complimentary transverse colostomy in selected cases. Those surgeons who have had wide experience with the abdominoperineal excision of the rectum are aware of the tremendous variation in the amount of blood carried to the rectum through the middle hemorrhoidal arteries. Many times these vessels are cut during the course of the dissection without the necessity of applying ligatures. Other times they are large, freely bleeding vessels supplying a large amount of blood to the segment in question. If, therefore, the superior hemorrhoidal vessels have been divided, as they should be divided for lesions whose lymphatic drainage accompanies these

vessels, it will frequently happen that the blood supply to the upper rectum to which the sigmoid must be joined will be questionable or it may be that under this circumstance there has been difficulty in properly placing the sutures and the surgeon may not have the complete confidence in the technical phase of the anastomosis that he would like. Under these conditions, it is our feeling that a loop of transverse colon should be brought out through a separate incision in the upper abdomen and the fecal stream completely diverted from the line of anastomosis. If such a procedure is carried out, it is then essential that before closure of the colostomy, the line of anastomosis be carefully examined by means of barium enema to determine whether or not there is a leakage around the suture line. If such leakage does occur, and it not infrequently will, the closing of the colostomy must be postponed until healing is complete; and in any of these cases we have seen up to the present time, healing has occurred spontaneously in 1 to 3 months.

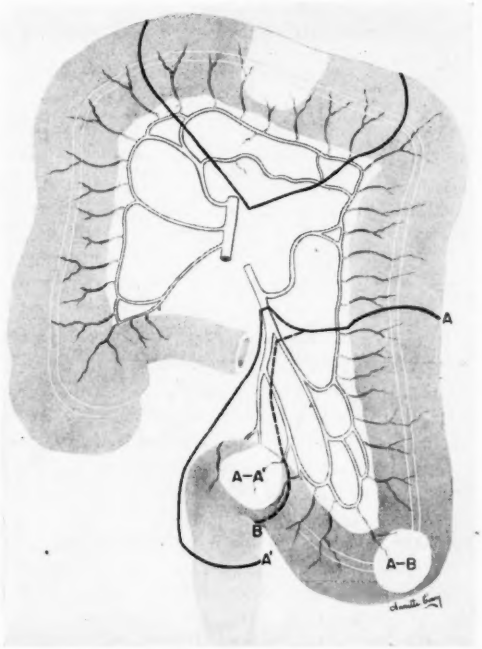

Fig. 5. Schematic representation of bowel and mesentery to be removed in carcinoma of transverse colon, at apex of long mid-loop of sigmoid, *A–B*, and lower sigmoid or rectosigmoid, *A–A'*.

TECHNICAL CONSIDERATION

Right colon. We have never used the exteriorization operation on the right colon. In the occasional cases in which patients cannot be properly prepared for a one stage procedure, we have used preliminary ileotransverse colostomy followed in 16 to 21 days by resection. In this type of case, we prefer lateral anastomosis in continuity to transection of the ileum. For many years following the teaching of D. F. Jones, we used the lateral anastomosis in our one stage procedures. This is probably the simplest and safest type of anastomosis that can be done. If the blind ends are short, they do not give symptoms and the functional results are completely satisfactory. More recently, we have been doing an open end-to-end anastomosis. Although the functional result is no better than when the lateral anastomosis was used, the anatomical result is superior and there is only one suture line to put in. If the lateral anastomosis is used, the medial side of the mesentery is closed before the anastomosis is carried out. If the end-to-end junction is employed, it is easier to do the anastomosis first, closing the mesentery after the anastomosis is completed. The lower portion of the right gutter is closed in all cases, but only rarely can it be closed throughout its entire length. Drainage is not employed unless there is persistent oozing or an abscess cavity has been broken into. Proper drainage is then instituted into the retroperitoneal area through the right flank.

Midtransverse and left colon. Wide acceptance of the exteriorization operations was probably the greatest single factor in increasing the safety of resection of the left colon. It has made possible safe intestinal resection in the hands of experienced and less experienced surgeons. However, there are definite disadvantages in this type of operation, and with the present development of patient care and technical surgery, I feel certain that these operations will rapidly diminish in popularity. I personally have done but one in the last 6 years. I feel concerned at times lest our resi-

TABLE III.—RESECTIONS WITH PRIMARY ANASTOMOSIS CAUSES OF DEATH—1942–1947

Operation	Age	Cause of death	Comment
Resection of transverse colon	78	Not known	Palliative operation—extensive local and metastatic disease
Reduction of intussusception and resection of sigmoid	78	Sudden—no cause found (autopsy)	
Resection of sigmoid	51	Peritonitis (clinical)	Palliative operation—extensive local and metastatic disease
Resection of sigmoid	46	Pulmonary embolism (autopsy)	Was ready for discharge—small local leak had spontaneously closed

dent staff at the Massachusetts General Hospital not know the technique of this procedure, as it is now so rarely used in that institution.

The operation of choice for the writer in a lesion at or beyond midtransverse colon is an adequate removal of the bowel and mesentery with a direct end-to-end anastomosis. My own preference is for a closed type of anastomosis,[1] using the Parker-Kerr technique. We prefer the basting stitch to the use of instruments, since in our hands it is more flexible, is always available, and can be used lower in the pelvis than instruments. We have personally had no difficulty in the formation of a diaphragm or with any other form of obstruction at the site of the anastomosis. Care is taken not to narrow the diameter of the bowel during the placing of sutures and to be sure that the diaphragm is adequately broken down after the basting stitches are removed. We use a No. 1 plain catgut for the basting stitches, a continuous No. 000 chromic catgut suture for the inside, and interrupted No. 70 cotton for the outside layers. When possible, the suture line is protected by means of omental tabs or by means of omentum. Drainage is not used unless there is some specific indication, as suggested above. The mesentery is always carefully closed medially, but when the left colon is completely mobilized, the remaining bowel falls back into the raw area in the left gutter, and no attempt is made to close this with peritoneum.

There is an increasing trend toward use of open anastomosis, and the recent report of Allen, Welch, and Donaldson gives support to the safety of this method. It is not the method but the care with which the operation is carried out that is of major importance.

I do not use chemotherapeutic or antibiotic agents locally or systemically. It is my feeling that if the requirements for direct anastomosis have been fulfilled and the operation has been carefully done, the anastomosis will function properly, there will be no leakage, and there is little danger of peritonitis. If the blood supply is inadequate or if the sutures have not been properly placed, there will be leakage and serious results may follow. Bactericidal agents will not compensate for either. I am not convinced that intestinal antiseptics play as important a part in intestinal surgery as does careful preparation of the bowel and of the patient as already discussed. While I do use sulfasuxidine or sulfathalidine in the preparation of the bowel before operation, I still consider the bowel contents as actively infectious as though no drug were used. I hold but one thought—restitution of bowel continuity through a carefully done anastomosis independent of any other help.

Postoperative care. The postoperative management of these patients is very simple. A transfusion of 500 cubic centimeters of whole blood is usually given on the table during the course of the operation. If there has been undue blood loss during the procedure, additional blood is given to replace the loss. The patient is allowed liquids without milk or fruit juices during the early period of healing, aware that the line of anastomosis is probably weakest at the end of about 4 or 5 days. On the fifth day, milk is allowed in the diet. Following that, it is rapidly built up to an adequate diet low in residue. The rectal tube is inserted at frequent intervals to permit the release of any gas which might collect in the rectum. Morphia or pantopon is given freely for any discomfort. Supplementary fluids are given by the parenteral route if the oral intake has not been adequate, and it usually is not for the first 3 or 4 days. Vitamins C and B complex group are given intravenously in 5 per cent glucose in distilled water or in saline, as the indications may be. One thou-

[1]The closed anastomosis is not a suitable method after resection for diverticulitis, nor do we use it in anastomosis of small bowel.

sand cubic centimeters of 5 per cent amigen or its equivalent in dextrose is given daily for 4 or 5 days. A hematocrit or hemoglobin determination is made 48 hours after operation. If the hemoglobin is below 13 grams per 100 cubic centimeters sufficient blood is given to bring it above this level. If the Levin tube has been used, we rarely leave it in place more than 48 hours after operation because of the inability of the patient to utilize fluids taken by mouth with the tube in place. If the Miller-Abbott tube has been used and is well down, the patient can be given fluids as desired and will utilize them. If the patient tolerates the tube well, it is left in place until gas is being passed freely by rectum. If on the other hand, the patient is greatly bothered by the tube, we have no hesitancy in removing it after 24 hours. We do not use sulfasuxidine after operation. In most cases the bowels will move spontaneously by the sixth day; if they do not move by this time, milk of magnesia, 10 cubic centimeters, every hour for 3 doses, is given. The patient is usually discharged 10 or 11 days after resection.

RESULTS

The immediate results following resection of the colon for cancer are given for the past 16 years, the year 1942 being used as the transition year from the earlier to the present methods (Tables I and II). More striking than the drop in mortality rate is the transition from staged operations to resection and primary anastomosis, proximal decompression being reserved for those who were admitted with advanced obstruction or where a difficult anastomosis had been performed low in the pelvis and there was some doubt as to the security of the suture line. The mortality rate of 3.6 per cent for the 110 operations in which a primary anastomosis was done seems to justify a continuance of the present methods.

Discussion of fatal cases following primary anastomosis (Table III). The 2 patients who died following resections for extensive local and metastatic disease need no comment. The 78 year old woman, whose sigmoid growth had intussuscepted, who was operated upon with obstructive symptoms and without proper preparation, and for whose death no adequate cause was found, should probably not have had a primary resection with anastomosis. Better judgment might well have avoided this fatality. The fatal pulmonary embolism occurred in a young woman with a somewhat difficult low anastomosis. Autopsy showed necrosis of a short segment of the suture line which had spontaneously healed by agglutination of the open area to adjacent structures. Quite possibly this local fault contributed to the formation of the fatal thrombus. This represents either a technical error or error in judgment in not recognizing the possible faulty anastomosis and performing a proximal colostomy.

SUMMARY

Several of the more important contributions to resection and anastomosis of the colon for cancer have been reviewed.

Principles for resection and primary anastomosis are presented.

Results following resection in the decade before 1942 and in subsequent years are given.

The trend toward resection with primary anastomosis is shown and mortality rates given which would seem to justify this change.

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THE EFFECT OF HEPARIN ON WOUND HEALING

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IN 1940 in this laboratory evidence was presented by controlled experiments that heparin will prevent the reformation of peritoneal adhesions (5). It was postulated that this effect is due to the prevention of the formation of fibrin in the peritoneum into which fibroblasts could grow. If heparin has this effect in the peritoneal healing process, a similar effect might occur in wounds by the prevention of the formation of a fibrin scaffold for fibrosis with resulting delay in the increase of wound strength. Since heparin is used freely in postoperative cases, any such result should be known. The work herein reported was interrupted by the war and only recently completed.

Murray, in 1938, pointed out that heparin apparently did not inhibit the healing of incisions in blood vessels, although no measurements were made. Bendix studied the effects of heparin on the healing of gastric incisions, finding no effect on the fifth postoperative day. Laufman and Heller, in 1943, reported no essential difference between the tensile strength of abdominal incisions in dogs receiving heparin postoperatively and a comparable group of control animals. Several investigations have shown an inhibitory effect of heparin on growth of embryonal and tumor tissue in culture media (2, 3, 7).

METHODS

In these experiments, rabbits were used weighing 5 to 7 pounds. Under nembutal anesthesia and aseptic precautions, a right rectus incision was made. The stomach was brought up into the incision and a segment of the anterior gastric wall grasped with an atraumatic clamp. The anterior gastric wall was incised for a distance of 2.5 to 3.0 centimeters, and the incision was closed with two layers of fine cotton. A Connell stitch was used for the inner layer and interrupted mattress sutures for the outer. The abdominal incision was then closed in three layers, with three continuous fine cotton sutures—one for the peritoneum and posterior rectus fascia, one for the anterior rectus fascia, and one subcuticular stitch for the subcutaneous tissue and skin.

Two series of animals were followed: one control and one experimental. The operative procedure was identical in all of the animals. All were fed a standard laboratory diet, including green leafy vegetables, and received 100 milligrams of vitamin C subcutaneously each day, beginning with the day of operation. The experimental group received ½ cubic centimeter of heparin[1] intravenously and 1 cubic centimeter subcutaneously immediately after the operative procedure, following which they were given 1 cubic centimeter of heparin subcutaneously every 4 hours until the time of sacrifice for wound testing. It was found that this massive dose of heparin was required to assure continuous and marked prolongation of the coagulation time in the animals, from the time of closure of the abdominal wall to the time of wound testing.

Plasma proteins were determined by the micro-Kjeldahl method on each animal preoperatively and at the time of sacrifice.

Groups of animals in each series were sacrificed at intervals of 2 days beginning with the second and ending with the fourteenth postoperative day. The stomach wound was tested by excising the stomach, ligating the orifices, and inflating it with compressed air until rupture occurred either through the wound or in the normal stomach wall. The pressure in millimeters of mercury at the time of rupture and the site of rupture were recorded. One centimeter strips across the abdominal incision, including all the layers of the abdominal wall and the contained suture

From Surgical Research Laboratory, University of Virginia Hospital.

[1] 1100 Toronto units per c.c.

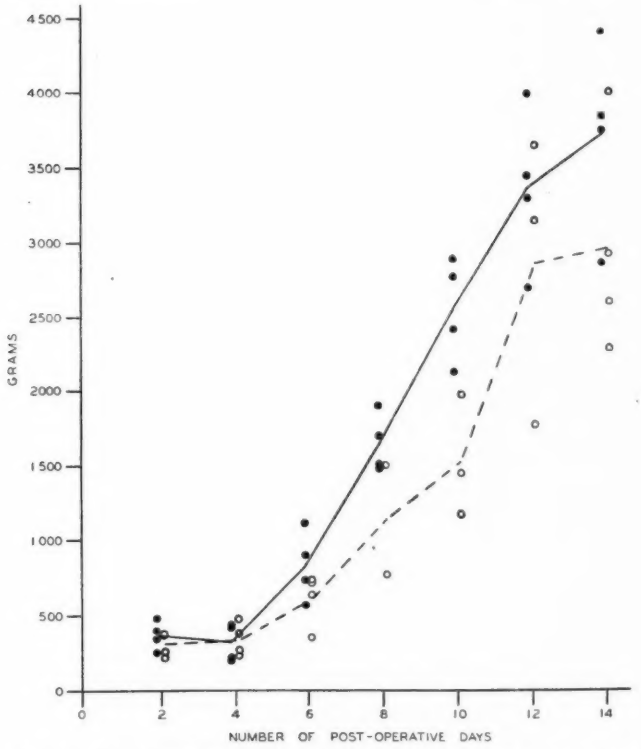

Fig. 1. Wound tensile strength, individual and average. Black dot, control average; circle, experimental average.

material, were tested by suspending the strips between two clamps and adding weight at a constant rate until disruption occurred. The disruption weight was recorded in grams. Two or more one centimeter strips from each animal were tested, and the average of these several values was taken as the tensile strength of the wound. Since the continuous sutures were divided at each border of the test strip, they pulled out without influencing the breaking strength of the wound. The data obtained were subjected to statistical analysis in the case of the abdominal wounds.

Numerous animals died on the first to fourth postoperative day, 17 out of 40, or 42.5 per cent, in the experimental series and 7 out of 35, or 20 per cent, in the control series. In the control series the causes of death were the effect of anesthesia or hemorrhage from cardiac puncture done to collect preoperative blood samples, while in the experimental series death occurred from these two causes as well as hemorrhage from the gastric wound, although careful hemostasis was carried out. No animals that showed gross evidence of hemorrhage either in the general state of the animal or by pathologic findings were used in the evaluation of wound healing in either the control or experimental series. The control group contained 27 satisfactory animals, and the experimental, 23.

RESULTS

The tensile strengths of the abdominal wounds (individual and average) for the control and experimental series are shown for each time interval in Figure 1. The average tensile strength of the abdominal wounds of

TABLE I.—GASTRIC INCISIONS

No. days	Control Series		Experimental Series	
	At wound mm. Hg.	Not at wound mm. Hg.	At wound mm. Hg.	Not at wound mm. Hg.
2	66			
	46	60	60	60
	66			
4	54			
	50		60	54
	42		58	
	40		60	
6			50	
		46	66	
	74	90	48	
		66	54	
8	84	76		76
	70	64		90
10	64			
	76		60	
	66		110	
	80		78	
12		70	86	
		74	55	
		20	68	
14		74		
		62	62	70
		90	84	96
		67		

TABLE II.—PLASMA PROTEINS

Control Series		Time of sacrifice—days postoperation	Experimental Series	
Preoperative gms./100 c.c.	At time of sacrifice gms./100 c.c.		Preoperative gms./100 c.c.	At time of sacrifice gms./100 c.c.
5.65	4.85	2	4.76	3.68
5.60	4.75		5.07	4.66
5.48	5.15		4.61	3.87
4.58	5.13			
5.46	5.42	4	5.33	5.66
5.25	5.23		5.13	4.93
4.85	4.84		5.74	5.44
5.29	4.83		5.61	5.58
5.35	5.18	6	4.40	4.59
6.13	5.67		5.02	4.84
5.22	4.67		4.76	4.81
5.45	4.93		4.60	4.59
5.35	5.33	8		
5.12	5.42		5.10	5.49
5.48	4.06		6.10	5.28
4.78	4.82			
6.36	6.57	10		
5.91	6.09		8.12	6.95
6.13	7.17		6.60	6.00
6.13	6.75		6.17	5.94
6.45	5.63	12	6.46	4.56
6.27	6.16		6.02	4.94
6.57	5.85		6.46	6.41
5.45	5.56	14	6.36	6.30
5.80	5.72		6.04	5.07
5.60	6.26		6.20	5.74
4.90	4.69		6.85	5.43
5.58	5.44	Average	5.72	5.25

the control animals at each interval is 200 to 1,000 grams stronger than that of the corresponding wounds of the experimental animals, from the sixth through the fourteenth postoperative day. The individual wounds at each time interval of testing in the heparinized series are in general of lower tensile strength than are those in the control series, although the strongest wounds in the experimental series at each time interval are stronger than the weakest wounds in the corresponding control groups with the exception of the tenth postoperative day.

The results for the gastric incisions are shown in Table I for the control and experimental series. In the control series of 27 animals, there are 14 which ruptured at the gastric incision while 13 ruptured at some point other than the incision. In the experimental series of 22 animals, there were 16 which ruptured at the gastric incision while 6 ruptured at some point other than the incision. In considering the animals at the twelfth and fourteenth day, none of the stomachs in the control series ruptured at the incision. However, all of the stomachs at the corresponding days in the experimental series, with the exception of 2 in the 14 day group, ruptured at the incision.

The values for the plasma proteins, preoperative and at the time of sacrifice of the animals for the control and experimental series, are shown in Table II. In the control series, the average preoperative plasma pro-

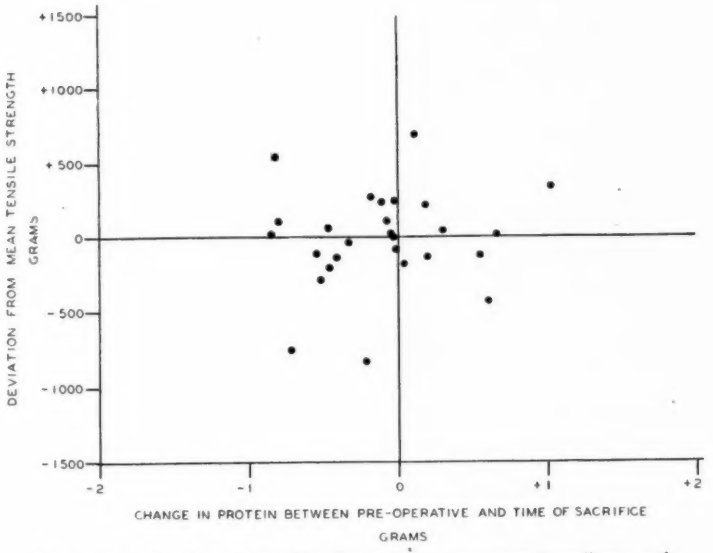

Fig. 2. Control series, relationship of protein to mean wound tensile strength.

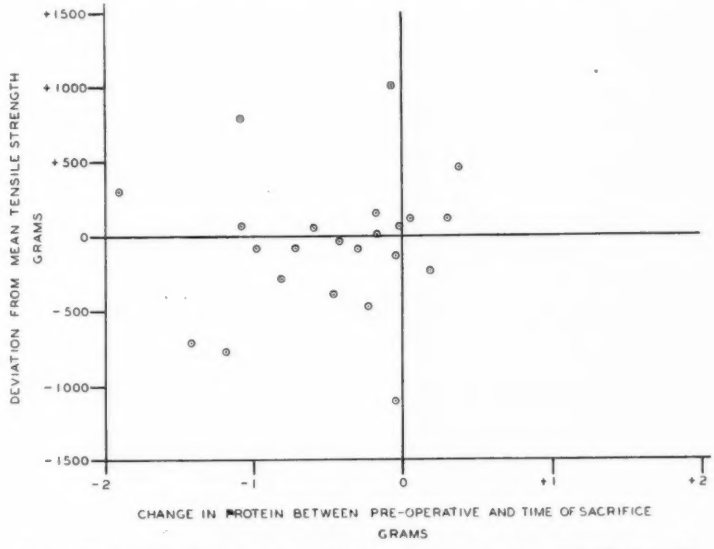

Fig. 3. Experimental series, relationship of protein to mean wound tensile strength.

tein for the whole group is 5.58 grams per 100 cubic centimeters, and at the time of sacrifice, 5.44 grams per 100 cubic centimeters; whereas, in the experimental series, the average pre-operative plasma protein is 5.72 grams per 100 cubic centimeters, and the average protein value at the time of sacrifice was 5.25 grams per 100 cubic centimeters.

DISCUSSION

In the evaluation of the results, when comparing control and experimental series of animals, the effect of the factors known to influence wound healing must be considered. It has been repeatedly demonstrated that proteins and vitamin C influence wound healing; therefore, the adequacy of the control of these two factors must be considered in determining the effect of heparin on wound healing.

In this experiment the animals of both series received the same diet and were given excessive amounts of vitamin C parenterally. It was therefore believed that the vitamin C factor was not responsible for possible differences in wound healing between the control and experimental series.

The protein levels in the two series were not so readily controlled because of unmeasured and variable blood loss, particularly in heparinized rabbits. In the control series there was an average plasma protein loss, between the preoperative period and the time of sacrifice, of 0.14 gram per 100 cubic centimeters. In the experimental series there was an average loss of 0.45 gram per 100 cubic centimeters. With the greater average loss of protein in the experimental group of animals, it is important to determine if there is any correlation between protein loss and wound strength in each series of animals. The effects of protein change on wound strength can be represented graphically by plotting wound strength deviation from the mean wound strength for each series of animals against the difference in preoperative and postoperative protein for each animal in the two series. In Figure 2 it is seen that in the control series there is no relationship between change in protein level and wound strength deviation from the mean, since the 18 animals having protein loss were equally divided as to wound strength above and below the mean. This same distribution above and below the mean is found in the animals showing a gain in protein. In Figure 3 the relationship of the change in plasma protein to wound strength deviation from the mean is shown for each animal in the experimental series. Although a greater number of the animals in the series showed a loss in protein, 8 of them having a loss had wounds of tensile strength above the mean. Therefore, the changes in plasma protein in the control and experimental series did not influence the wound strength in either series to an appreciable degree.

The differences in wound strength found between the control and experimental series is not great, but one of statistical significance on analysis.

Although not statistically controlled, the fact that in the experimental series as compared with the control series a larger proportion of stomachs ruptured at the wound instead of through the stomach wall tends to confirm the unfavorable effect of heparin on wound healing as demonstrated in the abdominal wounds.

CONCLUSIONS

1. In the heparinized series of rabbits, the wound strength, 6 to 14 days after operation, is less than in the nonheparinized series. The difference is statistically significant.

2. Twice as many heparinized rabbits died postoperatively, before the time of sacrifice, as nonheparinized rabbits. This fact introduced a possible selective factor into the experiment.

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PRESERVATION OF FUNCTION IN CYSTIC AND SCLEROTIC OVARIES

Report of Sixteen Cases of Single Ovary

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THE function of ovaries embarrassed by cystic and sclerotic disease need not be lost because of the inability to dispose of offending follicles. With a proper understanding of the pathology it is possible to explore these organs and preserve or perhaps even improve their utility. The statement has been made that since cystic follicles are generally distributed throughout the entire ovarian stroma, complete resection of the cysts is impossible without oophorectomy, and furthermore would be ineffectual even if accomplished, as it is obvious that the original trouble lies beyond the ovary (11). It would seem that if the original trouble was always outside the ovary when polycystic disease exists then both ovaries should be similarly affected, whereas actually one ovary is involved while the other remains clear just as often as both ovaries are attacked.

To prove clinically that such ovaries are amenable to surgical therapy I believed it necessary to demonstrate on single impaired ovaries that they were capable of resuscitation. Then there would be no question of controls or whether one ovary was carrying all the burden when two are present. The opportunity was presented by the overwhelming failure of surgeons to persevere with the many conservative gynecological measures like the extended myomectomy and cystectomy of Bonney (3), and Falk's tubal division for salpingitis, which reduce to a minimum the need for removing any part of the internal genitalia, particularly in young women. But as this pernicious and mutilating practice continues unabated, I have taken advantage of it in those instances where one ovary has been left behind, to deny that it is impossible to take away all the enlarged follicles without removing the ovary and to sustain the principle that when follicles obstruct the circulation and innervation especially where these enter the organ, the ovary may be given a new start and restored to usefulness after these hindrances are removed. This applies not only to ovaries enlarged by polycystic disease, but more especially to the apparently normal ovary which contains indistinct and inconspicuous threats to its function.

Although the operation has been done on 155 patients, only 16 form the basis of this report. They are women who have only one ovary, since both tubes and the other ovary had been removed, presumably for pelvic inflammatory disease. At intervals of 1 to 9 years this single remaining ovary became not only inadequate, but also disabling, forcing these patients to seek relief. Instead of removing the crippled organ, an attempt was made to restore its dynamics so that complete castration with its attendant evils could be averted. Its success has surpassed my expectations, and, since the therapeutic armamentarium including endocrine and psychiatric therapy was exhausted before surgery was suggested, it is logical to presume that the operation was the sole reason for the results obtained and should be applicable with even more benefit when both ovaries are present. This procedure therefore is presented as another aid in preventing the deplorable and contemptuous treatment of the female genitalia that is still so prevalent, and to support the position that in the surgery of the ovary excision should be the last and certainly not the first resource for the gross irregularities so frequently encountered.

The results in the 139 patients with two ovaries have been worthwhile and will be the subject of another report. Of these, 36 were patients with previously diagnosed ovarian disease, while in the remainder the procedure

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was part of some other operation which required entering the pelvis. However, with the exception of size the pathology differs in no way from that of the 16 cases of this report although in the latter the scars, adhesions, and contractures of the previous operation increased the difficulty of the exploration and intensified the cortical fibrosis.

PATHOLOGY

Farre, in addition to being the first to describe that important but neglected area of the ovary which he designated as the "white line," pointed out that an ovary which appears to be normal may indeed have one-third to one-half of its volume occupied by what he termed "morbid follicles." As he put it: "The morbid follicle occurs as a single cyst in the midst of otherwise healthy tissues. Although occupying more than one-third of the entire ovary it scarcely disturbs the even outline of that organ. Its coats are of uniform thickness throughout. There is no attenuation or preparation for dehiscence at any particular spot nor external sign of increased vascularity in one point."

These follicles do not rupture, nor do they regress rapidly and thus become an impediment in the mechanism of cyclic activity. But their consequence varies with position and if they happen to be placed near the mesovarian border beneath the thick unyielding cortex of the white line, the circulation and innervation are obstructed right where these enter the ovary. The circulation is compressed not only between follicles and the cortex, but also between the follicles themselves thus preventing the formation of a collateral circulation.

This is no rare occurrence. It happened in every one of the 16 cases of this report and in 60 per cent of the ovaries of normal size in the remainder of the series. In fact only one ovary of the 16 was enlarged, and that was by a hemorrhagic cyst. This frequency raises the question of whether the normal ovary can be recognized from a casual inspection of its exterior.

The ovary can, of course, be expanded by multiple cysts or multilocular and single cysts so huge that the ovary becomes a mere appendage of the tumor. These are not considered in this discussion as this study is directed more at ovaries which are of normal size and configuration, but whose function is impeded by difficulties it cannot overcome. The essential principles of ovarian exploration can be applied to these swollen ovaries with equal benefit and the ovary can be retained as a functioning unit.

Microscopic evidence of circulatory interference inside the ovary has been published elsewhere (9). As none of the ovaries of this series were removed, I can add nothing to what already has been described. Continued study of the ovaries taken out by others confirms this picture.

Grossly, while the follicles are clearly apparent, pathologists seldom see the true state of affairs. In the living person the line of demarcation at the hilum of the ovary, where the vessels make their transition into it, is distinctly defined since there is an abundant circulation in the mesovarium which contrasts sharply with that in the ovary below. Moreover there are often extensions of the disease in the mesovarium above, which arise from follicle changes that mischance has brought to the ovary just below the white line. It is only by putting the mesovarium under tension while it is still in place that the presence of this scarring above the line can be used to locate a malevolent follicle below it. The intra-ovarian stresses disappear also when the ovary is disconnected from the circulation. What may seem to be a flaccid organ out of the body can have areas of increased pressure when within it that may really be the deranging forces.

These concealed tense follicles can be the source of ovarian pain even when there is no enlargement or evidence of adnexal disease. While this pain usually radiates to the thigh or sacroiliac region, it may simulate the symptoms of appendicitis especially in teen-age girls. Failure to detect such follicles are the cause of numberless appendectomies, which are succeeded by oophorectomy with its distressing sequelae. It is not unlikely that they play some part in certain cases of dysmenorrhea and intermenstrual discomfort. The favorable and sometimes dramatic results of exploring apparently normal and obviously abnormal ovaries has led me to this conclusion.

A follicle expanding in or near the region of the white line provokes a more intense fibrotic reaction of the cortex there than at the free ovarian border. Corpora albicantia are often found in this area, but as pointed out by Allen, maturation of a follicle is not required for them to come into being. The fibrotic processes surrounding these bodies, however, tend to contract the ovarian cortex toward them even more than around follicles. In the larger series I found on four occasions definite follicles between the folds of the mesovarium itself. These had the appearance of ovarian follicles but may have been derived from the parophoron. The displacement of vessels could be seen easily, but as this was taking place in soft tissues it was having little effect on the circulation.

Thus, at the white line which is the junction of the peritoneal endothelium with the ovarian epithelium and is literally the life line of the ovary, there is greater prospect for adversity. Dissection of this part of the cortex from the stroma beneath is much more difficult than from any other part of the ovary as the two surfaces are held together by strong fibrotic bands through which vessels and nerves must pass. A follicle maturing between these surfaces has less freedom and at the same time excites a more intense cortical reaction here than anywhere else. Nor is this reaction limited to the outline of the follicle. It reaches down over the ovary and up into the mesovarium, in the meantime squeezing the vessels passing through it, not only by contracting but also by occupying the spaces assigned to the blood supply. This is manifested frequently by hypertrophy of the white line which seems to embrace the hilum with a strangling band. If the fibrotic infiltration has not advanced too far, engorgement of the ovary will take place when this tight stricture is released.

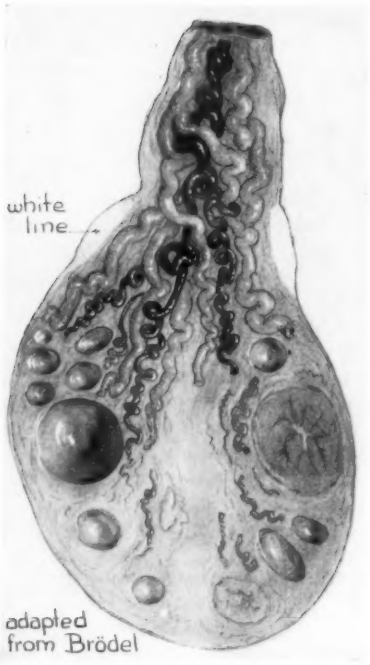
In ovaries enlarged by polycystic masses, the white line, or, for that matter, the remnant of the ovary itself is so hidden in the whole spread of that structure that it is hard to find. But the white line is quickly revealed if the suspensory ligament is traced down from the uterus as it will lead directly to this line and the ovary, no matter how small or indistinct that may be. The ovary will usually be found so compressed as to be practically useless, yet it may contain many cells which, while barely subsisting because of the compression, are capable of being revived.

ETIOLOGY

The removal of one ovary is often justified by the fact that one testicle, one kidney, or even one lung will do the work of two if too great a burden is not put upon it. The difference in the character of physiological function is, however, completely disregarded. Of all the endocrine glands, the ovary is the only one which does not maintain the same physical unity continuously. Not only physiological changes of the hormones, but variations of physical forces inside the ovary, caused by the incessant rise and decline of follicles, are constantly going on. One ovary is not adapted to the measured beat of the menstrual cycle that normally requires two. There is yet no proof that the ovaries alternate in ovulating, but clinical experience provides enough signs and symptoms to indicate that they do. When one carries the burden alone, cyclical rotations are taking place with such excessive rapidity that the ovary cannot accommodate them. Hence the ovarian stroma becomes enmeshed in a mass of follicles from which it cannot extricate itself, culminating finally in endocrine inadequacies and discomfort.

The endocrine aspect also must be considered in conjunction with the fluctuating forces inside the ovary. The decrease in total ovarian mass is followed eventually by a decline in the output of estrogen and progesterone, which are essential not only for the systemic metabolism, but also for that of the ovary itself. When the demand for either cannot be met, the basis for a vicious cycle is prepared since the two hormones reach their greatest magnitude at different times and the activity of one is largely dependent on that of the other.

With the remaining components of the menstrual cycle still operating, the single ovary, beset by internal physical difficulties and external endocrine stimuli, cannot survive for long the struggle to perform its function. Nothing can be expected from endocrine



Figs. 1 to 4. Drawings illustrating the mechanism of vascular occlusion at the ovarium hilum.

Fig. 1. Cross section of the normal ovary. Note that in the normal ovary the vessels are unhampered, that the maturing follicles are near the surface and that the circulation is able freely to traverse the hilum in both directions.

Fig. 2. A large follicle located right where the vessels enter the ovary. There is no indication on the surface of its presence and it could hardly be discovered by palpation. The vessels are caught between the enlarging follicle and the unyielding tunica albuginea. It is doubtful if a collateral circulation can develop with sufficient rapidity to prevent damage to some of the ovarian stroma beneath.

therapy when the changes in the ovary have become firmly established.

There is little actual data on the percentage of women with only one ovary who eventually required the removal of the other, but there is plenty of evidence that this practice has been and still is severely condemned. Caffier reports that two-thirds of a series of women who have had one ovary removed eventually got into further difficulty with the remaining organ. If that statement be true then this series of cases represents only 24 previous operations. The 16 first operations were carried out by different surgeons who were working in as many localities.

Howard A. Kelly, commenting on oophorectomy remarked: "The surgeon must bear in mind that his relationship to his patient is not dissolved with the successful performance of an operation—and he must decide if the remote sequelae of operative interference may be even more distressing to the patient than the present pains since she might become disabled in most relations of life. Proper surgery depends upon the recognition that what were once considered diseases of the tubes and ovaries are in many instances no diseases at all."

Arthur E. Hertzler was even more eloquent. He said:

"It has always been a mystery to me why surgeons should regard the castration of the human female with indifference, even derision. Even now women come to the clinic in droves who have had ovaries removed and were wrecked by it. But fortunately the science of mediums constantly advances. Formerly it was the surgeons who castrated their patients; now it is the roentgenologists.

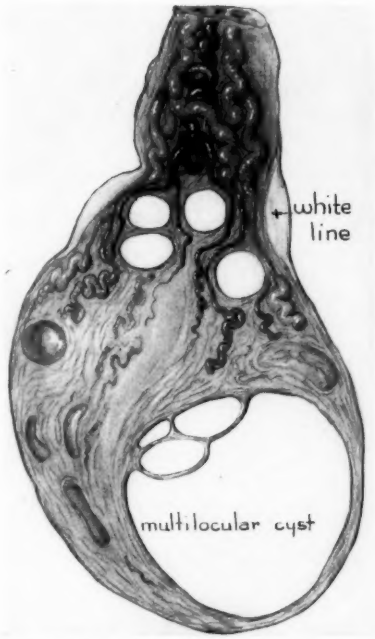


Fig. 3. Multiple small follicles in the ovarian hilum and a large unruptured one at the free border. These larger follicles which are usually emptied by just puncturing them may contain several smaller cysts any one of which can go on to occupy the space thus created. The smaller follicles in the hilum interfere with the circulation not only between the cyst wall and the cortex but also between the follicles themselves. Sometimes these extend along the whole length of the ovary between the white lines.

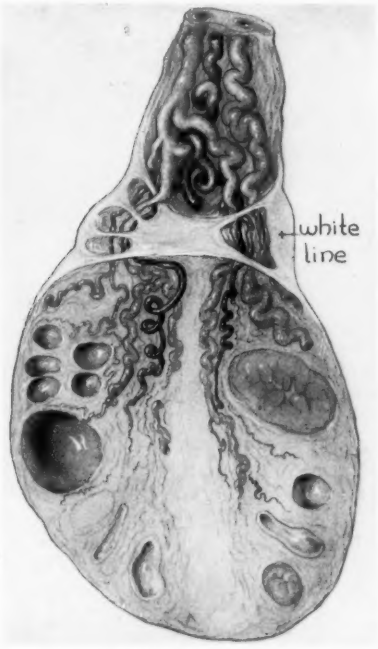


Fig. 4. A corpus albicans in the hilum. The reaction around these is greater than around follicles with clear fluid. Fibrous bands sometimes extending up into the mesovarium can be seen often with the naked eye and the cortex is firmly attached to it. Any combination of these conditions can be present and as there is little likelihood of either the follicles or corpora albicantia regressing in this strategic location, they more or less permanently alter the structural pattern of the ovarian stroma.

"I will have no more of it. There is not a lesion in this chapter (Involutional States of the Ovary) which can be maintained as pathologic to a degree that justifies removal and none in which the removal of an ovary but makes the last state of the patient worse than the first. The difficulty is due to the attempts to solve problems by detached study. The pathologist describes what he sees; the surgeon in the simplicity of his faith in the infallibility of pathology accepts the symbols of speech literally and cuts. The microscope does not reveal function. The physiological phase of the ovary can be determined only by study of the living. The study of the patient before and after removal of the ovaries is the only way in which one can determine their relationship to the well-being of the patient. Some of the most intense reactions I have observed occurred in women who had their ovaries removed after the cessation of the menses."

Many more of equal eminence could be quoted, but as I stated, little heed is given to their admonitions. Although these men do not tell what happens to the remaining ovary when the other is taken away, they imply that the remote effects are disastrous. The reason is that the single ovary becomes structurally incapable of carrying on continuously since it cannot cope with a pace that is too swift and a demand that is too great for its slow moving mechanisms.

The dynamics of ovulation are still obscure. Even though it is a process stimulated by an endocrine synchronism, physical forces play a large rôle in its execution, constantly changing the distribution of intraovarian pressures. The idea that during ovulation only one follicle enlarges is denied by Strassman. He stresses the point that several follicles around a focus expand, but only one goes on to ovulate

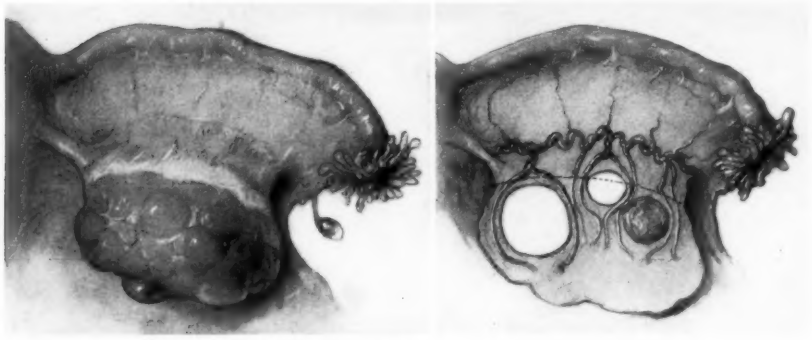


Fig. 5.

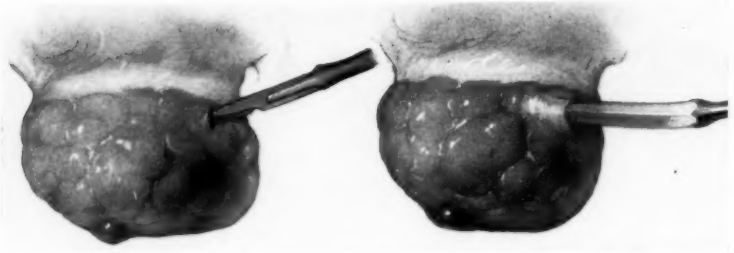


Fig. 6.

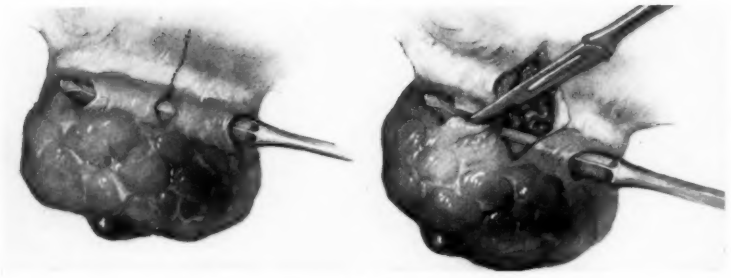


Fig. 7.

Figs. 5 to 11. Technique of ovarian exploration.

Fig. 5. An apparently normal ovary without any sign of trouble within it. However the transparency depicts two follicles and a corpus albicans in the hilum with vessels caught between them.

Fig. 6. A short incision is made at either border not quite through the cortex just below the white line. The incision is completed with the end of the tonsil knife while the blade is held parallel to the cortex. The flat of the blade sinks into the stroma separating it from the cortex and the knife is thus accurately placed between these two structures. The knife is then passed across the ovary to the other border, overcoming any resistance while the curved end is held against the cortex. A small incision is necessary sometimes to allow the knife to emerge because the ovarian capsule may be too tough for it to come through.

Fig. 7. An incision is made over the knife at the middle of the ovary and is then stretched by a small pointed clamp to open the mesovarium. The use of a knife here would cause too much bleeding. The point of the clamp is placed just beneath the peritoneum of the mesovarium which can then be incised with but little hemorrhage occurring. The cortex is opened along the length of the knife which is withdrawn.

because a one sided proliferation of the theca interna of this follicle forms a cone directed toward the surface of the ovary. This cone, which is wedge-shaped on the cut surface, in-

Fig. 8.

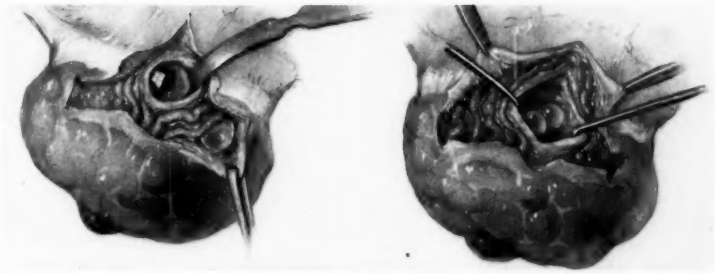


Fig. 9.

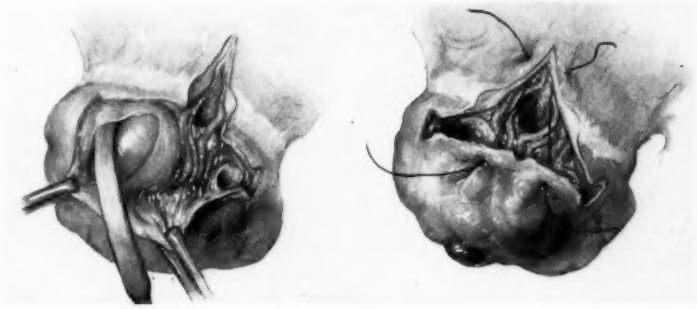


Fig. 10.

Fig. 8. The white line is grasped with Allis clamps and the end of the tonsil knife used to dissect the cortex off the stroma. It should be separated into the mesovarium. If the dissection is done accurately there will be little bleeding. This part of the cortex may then be removed. Follicles which otherwise have escaped detection can easily be palpated with the forefinger. It is not difficult to distinguish a cyst from a corpus albicans. The former feel like soft balls, while the latter are harder and their outline is not as distinct. The corpora are not excised but merely broken up so the ovary can absorb them.

Fig. 9. The middle cyst is enucleated. The stroma over the follicle is separated and the cyst shelled out. Note the two smaller cysts behind it. Puncturing will suffice for these.

Fig. 10. The largest follicle is enucleated. No harm is done if it does not come out intact but one must make sure there are no other follicles. Openings in the stroma should always be made from the mesovarium to the free border parallel with the vessels. There will be little bleeding. The cortex is sutured to the peritoneum of the mesovarium making a new white line and widening the mesovarium. If there is bleeding more sutures may be required but there is seldom need to completely close this opening. Fine catgut on atraumatic needles should be used.

filtrates and penetrates the surrounding tissues, thus making a path for the chosen follicle. The actual rupture, after the follicle reaches the surface of the ovary and protrudes beyond, is caused by the cessation of proliferation of the theca cells, while the membrane be-

Fig. 11. The normal position of the uterus and its adnexa. Illustrations in textbooks convey the impression that the tube is above the ovary and the latter exposed to the peritoneal contents while all are spread out over the width of the pelvis. This sketch is presented to show the ideal location of the tubes and ovaries but of course this could not be attained in any case of this series because no tubes were present. This relation of the tube, ovary, and broad ligament may account for the absence of adhesions to the ovary although raw surfaces due to ovulation are constantly being exposed. While this may not be the true reason, placing the structures in this relation after surgery of the ovary will prevent adhesions. The ovary should be well out of the cul-de-sac. This is usually accomplished by suspending the uterus according to the Baldy-Webster method.

tween the interior of the follicle and the peritoneal cavity becomes progressively thinner. Circulation on top of the vertex of the graafian follicle is interfered with by internal pressure, and the capillaries do not contain blood cells inducing atrophy. The slowness of the process permits the rupture to take place in a very smooth manner.

When this action goes on near the ovarian cortex or along the free border, little damage ensues if it is not completed. But when it takes place in situations that do not favor successful termination, the ovary will now contain a static body which is not readily discernible, yet can alter more or less permanently the entire internal structural pattern. This can, and much more frequently than is popularly realized does, happen without any enlargement whatsoever and with no indication on the surface of the ovary of the disturbed conditions beneath.

These locations are deep in the center of the ovary and high up in the hilum between the white lines. Here the accidents of nature and the elements of chance come into play. There is no way of predicting which group of follicles is to be selected for maturation, and it is pure misfortune when an adversely circumstanced one is picked. Exploration of such ovaries in the living quickly brings the realization of the futility of hormone therapy and explains some of the failures of this type of treatment in cases in which it would seem to have every opportunity to succeed.

ABSTRACT OF A CASE

Since all the patients presented a similar syndrome it would be needlessly repetitious to describe each one in detail. They differed from each other only in the prominence of a symptom or a sign. All the 16 women were between the ages of 25 and 33 and had had the first operation, when both tubes and one ovary were removed, from 1 to 9 years previously. Fourteen were white and two were colored. The diagnosis presented no problem, and indeed often was made by the patient herself.

A typical case history follows:

Mrs. C. L. C., white, age 33 years, was operated upon 9 years ago when both tubes and the right ovary were removed. She remained perfectly well for 6 years and her menstrual cycle and psychodynamic state were normal. Then she noticed that she was becoming more irritable and irascible, there was a reduction in the duration and quantity of bleeding, the intervals between periods became shorter and dysmenorrhea, which was often disabling, increased in severity. At times there would be a continuous spotting over a period of weeks. Occasionally she would have severe discomfort in her left side which apparently had no relation to her periods. Coitus became painful and her libido disappeared. Flushes had started during the previous year.

She was a tall, well developed, poorly nourished woman who lost her emotional control as she recited her history along with the fact that several doctors had informed her that the remaining female organs would have to be taken out. She had already received endocrine therapy. With the exception of the psychological disturbance no abnormalities were

found besides those pertaining to the genitalia. Tenderness, spasm, and rebound tenderness in the left inguinal region were present, but no masses were discovered. The cervix was slightly enlarged, and the uterus was normal in size, moderately retroverted, and sensitive. While no actual tumors could be made out in the left adnexal region some thickening was noted, and extreme tenderness was elicited with just moderate pressure.

At operation (January 8, 1945) the old midline scar was excised and the abdomen entered after many intestinal attachments were separated. Both tubes and the right ovary were absent and the pelvic peritoneum was thicker than normal. The left ovary was buried in a mass of adhesions, and when released was found to be about 1½ inches in diameter and under severe internal pressure. A cyst at the free border was inadvertently opened and found to contain dark grumous material. Several other small follicles containing the same matter were around the larger one. The mesovarium, which was on tension and partially twisted, was freed and the circulation to the ovary exposed. The hilum and mesovarium were then opened and explored. Several small follicles, each about ¼ inch in diameter and one about ⅝ inch in diameter along with one corpus albicans, were removed. These did not reveal themselves in any way along the surface of the ovary. To maintain the ovary in as favorable position as was possible under the circumstances and keep it out of the pelvis the round ligament was shortened and several reefing sutures were taken in the infundibular ligament. The abdomen was closed and the convalescence proceeded uneventfully.

She was discharged from the hospital in 10 days with instructions to return after the first period was over. She came in jubilant. The period lasted 4 days, was without pain, and the flow was much greater and of normal color. In a few months she reported again. Her constant emotional tension had disappeared and premenstrual distress was comparatively mild. Her libido was regained, the flushes and irritability vanished, and she increased 10 pounds in weight. In fact she presented an entirely different personality which seemed to emanate just as much from the disappearance of tension as from the relief of discomfort. She has continued to maintain this improvement up to the time this report was submitted for publication.

The others have been almost as fortunate, although the result was not obtained so quickly. Relief from suffering, restoration of the cycle, and emotional adjustment eventually was obtained in every one. One has endured for 3 years, but now has some menopausal symptoms at 34. Another began missing periods a year after operation, but now the regularity has returned. Three could not be traced more than 6 months, but the rest are without discomfort and are enthusiastic about the outcome.

TECHNIQUE OF OPERATION

Bonney, an ardent advocate of conservatism, states that "there is a pleasure, pride, and satisfaction in conservative operations which cannot be appreciated save by those who have performed them . . . but it requires of the surgeon that he should forego a procedure which achieves a striking result in a startlingly short time for one which, though it takes longer, has far greater appeal to the connoisseur" (4). This certainly applies to ovarian exploration. Judging from the results of the whole series of cases, sometimes disappointment and failure were converted to success only after several months had elapsed.

This operation is not the same as the ovarian cystectomy of Bonney, the decortification procedure of Reycraft, the splitting operation of Bailey, or Stein's excision of a wedge at the ovarian border. None of these attack the impeding factors at their source in the ovarian hilum between the ventral and dorsal white lines and all are more or less empirical in their approach. While undoubtedly effective, they fail to recognize the pathology that may exist in the narrow and vital area where vessels and nerves make their transition from the mesovarium to the ovary, and provide no method for correcting it.

The first step in exploring the ovary is to examine the mesovarium observing particularly the number of vessels going to the ovary and the presence of varicosities. The latter are usually part of a general varicose condition of the broad ligament, and when present must be taken care of first. Because of the previous operation the mesovarium of every ovary in this series was distorted by adhesions, rotation, or malposition, and it required much manipulation to bring about the normal relationship again. Without previous surgery, the mesovarium is usually clear. Restoration of a straight mesovarium without deformity and with the ovary properly suspended is of supreme importance. This is often difficult and requires much finesse when adhesions between the ovary and whatever happens to be covering it are divided.

The ovary is held by the fingers, as instruments may do damage because of the friability of the tissues. A clamp is *not* placed across the

mesovarium to prevent bleeding since cutting off the blood supply, even for so short a time, reduces the internal stresses in the ovary and prevents accurate observation of the state of the circulation. If the operation is done properly the loss of blood is negligible, and I have not found it necessary to remove an ovary on that account, though more than 300 have been explored.

After the mesovarium has been straightened and the position and thickness of the white line have been noted, an incision about 3/8 inch long is made into, but not through, the cortex parallel and close to either border just below the line. A flat double edge tonsil knife with a round sharp end is then used to separate the cortex from the stroma. With the knife held in the same plane as the surface of the ovary, the end is placed in the incision and with a few short strokes the remainder of the cortex is cut through and the back of the knife sinks into the ovary against the stroma. Thus the blade is accurately placed between the cortex and the stroma. Holding the curved sharp end firmly under the surface of the cortex, the knife is passed across the ovary until the end can be felt near the opposite border, when a small incision is made over it allowing the end to come through. It is not easy to pass the knife across the ovary. One will be amazed by the density and firmness of the tissues, but by using the twisting movement of an oyster shucker and unhesitatingly overcoming any resistance, the cortex can be separated from its underlying stroma without injury to either.

Keeping the knife in that position, an opening is made about the middle of the ovary right over the knife, and a clamp is inserted into this opening pointing upward parallel to the vessels in order to spread this incision wide and dissect up under the white line and into the mesovarium just beneath its peritoneum. The cortex is then divided over the knife between the two end incisions and the knife is withdrawn. The hilum of the ovary is now exposed and the interior of the ovary is accessible. Unless bleeding is profuse, which seldom happens, no effort is made to stop it.

The edges of the open white line are grasped with Allis forceps and that part of the cortex is dissected upward and cut off. One must not cut too close to the ovary as blood vessels which are close under it might be severed. The finger is inserted into this opening and the position of the cysts or corpora albicantia, which cannot be detected through the intact cortex, can easily be discovered by palpation with the forefinger.

The latter are broken up with a pointed probe, but follicles should be enucleated if possible. This may be done with the sharp round end of the knife. If one bears in mind that the trabeculae of the stroma run parallel from the mesovarium to the free border and works only in that direction, there will be little bleeding and few ovarian cells destroyed. If it is not practicable to shell out the follicles they should be opened, but the aperture must be made adequate and sufficient to scan the interior to detect smaller follicles within.

Careful inspection of the wall of a follicle will disclose why puncturing rarely suffices for their complete disposal. The majority are not single follicles but a nest of several with one large and a few smaller ones. Piercing the large one merely permits it to refill or else allows one of the smaller ones to expand and occupy the space. Frequently what appears to be one large follicle may be a cluster of several smaller ones of almost equal size which together present the appearance of a single well rounded cyst.

It is not imperative that these structures be taken out. There is no pathological condition at hand that can be considered a disease. The effort is directed at relieving obstruction and strangulation. That is why partial resection of an ovary is silly. The part left behind still contains the same impediments and the only change has been an unnecessary and certainly undesirable reduction in the total ovarian capacity.

When the exploration is completed the ovary may be reduced in volume and one will often find that what externally seemed to be an ovary of normal size and shape actually consisted of only 1/3 stroma and the rest follicles of one kind or another. Hence to allow for possible expansion of the stroma the cortex should not be closed too tightly. Using fine catgut on atraumatic needles the lower border of the open cortex is joined to the open peritoneum

of the mesovarium so the latter becomes a straight line along with that of the cortex; in effect a new white line is created. Two sutures placed close to the apex of the incision into the mesovarium are usually enough and no more are needed unless there is oozing. Clamps, forceps, large needles or catgut and coagulation are avoided to prevent scarring. With the closure completed the ovary is now replaced and sutured as nearly as possible to its normal position and well above the cul-de-sac. In this series that could not always be done, but without the scarring and distortion of a previous operation it can usually be accomplished.

ADVANTAGES OF OPERATION

This procedure is not intended for those who do not have the remainder of the cyclic endocrine factors intact. It is not a substitute for, and does not provide follicle or pituitary stimulating hormones. Women who once have had the elements of periodicity and have suffered significant deviations are likely candidates. The ovary and endometrium should be considered in the light of final links closing the procession of events in the menstrual cycle. They play a major endocrine rôle too, just as important as others, but are much more liable to misfortune. Re-establishment of the ovarian link is the major objective for which fortunately these organs are accessible.

Nor should the operation be suggested until all other measures have failed to bring about improvement. In these 16 cases there was little likelihood of that happening, but treatment was attempted and was of no avail. When two ovaries are present the chance for a therapeutic result are, of course, much better.

Returning to the concept of the etiology and pathology I have depicted, it would seem that this operation would be futile aside from its value for this clinical study, since with only one ovary present the same abnormality is likely to recur. Perhaps that is true, but before the recurrence takes place the woman is that much further along toward the normal time for the menopause and her adjustment to it has made comparable progress. It has been my observation that the artificial menopause, when precipitated in young women either surgically or roentgenologically, is much more severe with more intense reactions than when it takes place at the proper age. A gain of 3 or 4 years is valuable and the probability of disruptions of the psychodynamic state is much less and in direct proportion to the number of intervening years. Hence the closer the time of the artificial menopause approaches that for the normal climacteric the less likelihood there is for physical and mental upsets. These women readily accepted the idea of preserving whatever is left of their ovarian function, and their continued enthusiasm over the outcome has not only been gratifying but signifies that their fervor is not the transient elation of convalescent patients. The results of ovarian inadequacy with its accompanying deprivation of estrogen is no light matter and is a constellation of emotion and feeling which the masculine mentality grasps only with the greatest difficulty, if indeed he does at all. If only he would match his zeal for preserving ovaries with that which he has for retaining testicles there would be much less repressed and concealed misery as a result of his gynecological endeavors. Although synthetic and natural hormones are available which can be administered to imitate after a fashion the normal cyclical variations, they are as yet only a poor substitute for those that are derived from within.

The popular surgical notion that the menopause when brought about prematurely reaches an end and takes place just that much earlier, is a cruel fallacy. The menopause does not terminate after having been artificially created until the natural span for that individual has elapsed. In the vast majority of such women who have come to my attention there are disagreeable sensations of discomfort at about the time the period usually takes place, to say nothing of permanent alterations such as the gain in weight and the change in personality. The latter cannot be dismissed as merely an intensification of psychic factors already in operation. Only the most phlegmatic escape, and then not entirely. Moreover at the normal time for the climacteric, after the patient has been tormented by these recurrent feelings perhaps over several years, a new set of symptoms appears and endures for many

more months. These consist mainly of severe flushes, headaches, vertigo, and emotional outbursts, but one such patient who had an artificial menopause at the age of 35, at 49 developed severe depression, hallucinations, agitation, paranoia, epistaxis, and dermographia. The syndrome eventually was controlled by adequate estrogen and psychotherapy, but for a while it seemed that sanatarium care would be required.

It is not generally recognized that excision of a tube may be the prelude to impairment of its ovary. Although it is thought the circulation is not injured, there is no way of knowing, because of the infinite variations, just where and how the anastomosis between the ovarian and ovarian branch of the uterine artery which usually carries the largest volume of blood to the ovary is maintained. In addition, after the tube is removed the ovary is drawn to the uterus by the sutures ligating the vessels of the broad ligament and thus the infundibular ligament containing the ovarian artery is put on tension. The creation of scar tissue and adhesions limiting the mobility of the ovary completes the picture.

And there is seldom need for removing a tube. Tubal disease, even in the face of widespread infection with purulent collections inside and outside the tube, is not an indication for salpingectomy. On many occasions, when the pelvic adnexa seemed to be one inflammatory mass, I have uncovered the medial ends of the tubes, evacuated their contents and divided and ligated them at that point. In addition it was necessary to maintain a stoma to prevent subsequent painful hydrosalpinx. So when the fimbriated end was closed, another opening was made somewhere along the tube. This was still less hazardous and certainly not as shocking as taking out a tube from friable, inflamed and bleeding tissues to which intestines usually were closely and sometimes inseparably adherent. Recovery has been so complete that little evidence of pelvic infection, either functionally or by examination can be found. It seems that the whole pathological process just melted away like the redness, swelling and edema disappear around a healing furuncle. And it is just as illogical to excise these inflamed tissues as cutting out the whole area of inflamed skin to heal a furuncle. Some of these cures have endured for 10 years. Even when the tube has been ruptured by an ectopic gestation it is necessary only to remove the latter, divide the tube at its medial end to prevent recurrence and sew up the bleeding area to control the hemorrhage.

Similarly there are but few reasons why an ovary should be removed. Among these are of course cancer and gangrene caused by twisting of the pedicle. Possibly it may be best to remove an ovary that contains a cyst so enormous that there is little likelihood of retaining any functioning part. But there is no need to take out an ovary or even part of an ovary for nonproliferative retention cysts, ovarian hematomas, dermoids or an ovary that has been shriveled by a fibrotic process. Falk advocates removal of a circumscribed tubo-ovarian abcess, but I have found even that unnecessary. Evacuation of the purulent material and division of the tube is all that is required. There is no way of predicting to what extent the ovary will regain its function after adventitious processes are no longer operating. Sometimes only a shell is left, but that part may contain enough cells to insure the continuance of function.

There is always the danger, when exploring an ovary, of uncovering a malignant or potentially malignant process and spreading it over the peritoneum. I have not encountered this yet and hence believe that while it is possible, it is highly improbable.

Exploration of an ovary is not difficult and need not be reserved for only those cases where the diagnosis has been made before operation. I believe it should be part of every laparotomy where these organs can be reached. With prudence and proficiency there is little to lose and much to gain. It is a means for giving a fresh start to an ovary which may seem normal, but yet is under the handicap of submerged follicles that give no indication of their presence on the surface. In these 16 cases there was no doubt of the diagnosis but their success was based on exploration of a much larger series of ovaries in the living and the concept of the pathology evolved out of the experience with them. A full apperception

of this pathology often will be the means of retaining ovaries and restoring them to usefulness even in the face of extraordinary lesions which at first blush seem hopeless. But it does require that the surgeon pause and devote some time to the study of the pattern of each malformation whether it be large or small before attaching the fatal clamps. And he must also bear in mind that he has not only the surgical means at hand, but also postoperative endocrine and other therapy which should be more than ordinarily effective since there will be fewer unknown factors to be reckoned with.

SUMMARY

Ovaries can be encumbered by follicles which, while they may or may not cause enlargement, do interfere with proper hormone production and ovulation. This is especially true when such follicles develop in the hilum between the white lines just where the vessels and nerves enter the ovary. This is not a disease, but rather a misfortune which can be corrected.

The opportunity to prove that these ovaries need not be removed has been furnished by the tendency of surgeons to disregard the many conservative gynecological measures designed to retain the internal genitalia, especially those that are so important to the psychodynamic stability of the female. A technique for accurately, not empirically, exploring the ovary is presented based upon a conception of the pathology that considers static follicles, either large or small as the malefactor. In 16 patients, from whom both tubes and one ovary had been removed, and the other had finally become inadequate, this remaining ovary was explored with results that demonstrate these organs can be restored to usefulness at least for a time, and need be wholly or partially excised only under exceptional circumstances. The success of the operation was demonstrated by the relief of discomfort, restoration of normal cyclicity and the return of emotional tranquility and personality adjustment. This procedure is presented as a conservative gynecological measure which can be applied to nonproliferative cysts of the ovary, the most common cause of ovarian failure.

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THE TREATMENT OF EMPYEMA WITH TOPICAL AND SYSTEMIC PENICILLIN AND OTHER ANTIBACTERIAL AGENTS

An Analysis of Twenty Cases

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IN 1943, Drs. John Lockwood and William L. White, representing the National Research Council, allowed us the privilege of participating on a project directed by Dr. White to determine the value of penicillin in preventing empyema following lung resection. This complication was frequent in spite of refinements of technique and the administration of sulfonamides, which had already greatly improved results. The remarkable protection afforded by administering penicillin systemically was soon proved on a small series of patients in whom resection had been done paired carefully with controls who received no chemotherapy of any sort. This work was published in 1944 (7). The complete protection of the treated patients compared with the routine occurrence of empyema in the controls led us to try topical treatment of empyema. We treated some spontaneous pneumococcic and staphylococcic empyemas with increasing success as we overcame the difficulties and improved the technique. With great trepidation we attacked a putrid empyema for which we had the profoundest respect. From sad experience we had come to classify this disease as a surgical emergency, next in urgency only to asphyxia and hemorrhage. We removed as much foul pus as possible and reinstilled 25,000 units of penicillin in 25 cubic centimeters of saline. We were so imbued with the need for early surgery in such cases that we intended to institute drainage the following day if there was still a foul odor to the pus. However, the following day there was much less pus, it was thinner and there was very slight residual odor. Of even more importance, the patient's toxemia and fever were considerably reduced, so that we continued with this form of therapy to complete cure in 16 days. The first 4 cases were included in the report of Lockwood, White, and Murphy (4).

At first, aspirations were often inadequate in amount or frequency or both, and the doses of penicillin instilled were small. In a few instances, culture became sterile quickly in spite of these errors, and cure fortunately resulted in spite of the failure properly to apply the basic principles of the treatment of empyema by any method. These basic principles are simple but absolutely essential: (1) evacuation of the pus, and (2) obliteration of the cavity. Any method which does not accomplish these ends is a failure. The few reports in the literature of aspiration treatment of empyema before the advent of penicillin indicated a great increase in morbidity and a definite increase in mortality by this method along with the frequent development of chronic empyema and of recurrences. However, good, though not perfect, results can be obtained by the method of adequate aspiration with reinstillation of penicillin pursued vigorously by one thoroughly acquainted with the surgical principles involved. Secondary, but very desirable, considerations are sterilization of the infected space and re-establishment of pulmonary function, which is accomplished only by re-expansion of the collapsed lung and pulmonary exercises. Resort to thoracoplasty is admission of partial failure. The method to be outlined can usually establish the required basic principles and the secondary considerations and can often greatly decrease the period of morbidity. It is essential for routine success that this method be used only by those whose extensive experience with the surgical treatment of empyema has taught them the

vagaries and elusiveness of pus in the pleura and the rapidity with which the lung can safely be re-expanded. Only such persons can recognize failure early and apply proper surgical drainage to accomplish cure and avoid serious complications.

RESULTS

Twenty patients with empyema were treated by aspirating the pus as completely as possible and instilling penicillin alone or with other agents into the cavity. Sixteen of these were cured by this method and 4 required surgical drainage. The ages ranged from 6 to 64 years, the empyemas were loculated in 18 instances and diffuse in 2, and the capacity, the amount of pus extracted at one tap, ranged from 18 cubic centimeters as a minimum to 1200 cubic centimeters maximum. Six were pneumococcic infections, 4 in pure culture, 1 associated with spirochetes, and the other with nonhemolytic streptococcus and Hemophilus influenzae; the latter was one of the failures. Nine others were streptococcic, 4 of them pure cultures of nonhemolytic streptococcus by aerobic and anaerobic culture, two nonhemolytic combined with hemolytic streptococcus, one each of nonhemolytic streptococcus with bacteroids or diphtheroids, and one was pure culture of hemolytic streptococcus. In 1 case only hemolytic Staphylococcus aureus was noted. One was a combination of Hemophilus influenzae, diphtheroids, and bacteroids, and was another therapeutic failure. The 3 others revealed no growth; however, the fluid was purulent grossly and cytologically and in 1 case smelled putrid. In 8 cases, the pus was putrid at the first aspiration. The average time of treatment, excluding Case 20, was 14 days with the longest time 33 days and the shortest only 1 day. The average number of aspirations for the 20 cases was 7.7 and varied from 1 to 18. The average dose of penicillin initially instilled into the cavity was 63,250 units. Seven of the cured patients received no penicillin systemically, although 3 of them had a continuation of sulfonamide therapy by mouth. In fact, one patient had been treated for 9 weeks before admission by repeated aspirations and the systemic administration of penicillin, without success. In 9 successful and all 4 unsuccessful cases patients received systemic penicillin, ranging from 100,000 to 300,000 units per day and averaging about 200,000 units divided into 12 equal 2-hourly doses administered intramuscularly. The pus became sterile after a single aspiration and reinstillation on 7 occasions, after 2 such maneuvers in 2 cases and was not noted in 1 other. Penicillin was not instilled on every aspiration in some of the earlier cases, and taps toward the end of treatment were unsuccessful at times. Bronchial fistula was proved in 8 of these 16 patients and healed without further specific treatment in all. In no case was the fistula a very large one which might defeat such method. A few of these 16 patients had been ill for several months up to 1 year (Table I).

Of the 4 patients who required further treatment, one showed Hemophilus influenzae which was not susceptible to penicillin, in 2 there were multiple loculations and the fourth was somewhat slow in improving, so was submitted to surgical drainage. These patients made a routine recovery after drainage, except for the one with Hemophilus influenzae in whom two instillations of streptomycin preceding drainage abolished the positive Hemophilus cultures but failed to improve the patient's condition. Her recovery, even after surgical drainage, was extremely slow, and the cause for this was never thoroughly explained in spite of repeated roentgenograms; bronchoscopies; cultures of sputum, bronchial secretions, of the empyema cavity, of the blood and urine; and vigorous supportive treatment.

No chronic empyemas resulted in the 16 successful cases, and pleural thickening, which was quite marked in some at the beginning, disappeared completely as shown by roentgenray and demonstrated in some of the examples depicted in this article. However, there were 2 cases in which there was persistent pleural thickening; in one biopsy was done as it was feared that a tumor might underlie the empyema. These patients have been followed for from 6 months to 3 years after discharge without further evidence of disease or symptomatology.

TECHNIQUE

1. Under adequate local anesthesia, locate a favorable site near the bottom of the cavity,

TABLE I.—SUMMARY OF CASES

Case Initials Age	Diagnosis	Etiology	Admitted	Discharged	No. taps	Units of penicillin instilled	Days treated	Units of systemic penicillin	Size of cavity cc.	Bacteriology	Sterile after	Broncho-pleural fistula	Results—Remarks
1 M. S. 47	Empyema, diffuse, right	Pneumonia	1- 2-44	2- 4-44	8	12,500	16	None	900	Pneumococcus, type 5	4 taps	No	Cured. Penicillin instilled only 4 times Sulfonamides systemically before empyema treatment begun.
2 A. R. 9	Empyema, diffuse, left	Pneumonia	1- 9-44	2-29-44	18	12,500	21	None	360	Pneumococcus	9 taps	No	Cured. Inadequate evacuation early. Small dosage.
3 A. S. 55	Empyema, loculated, putrid, right	Pneumonia 5 mos. before	3-10-44	4-12-44	15	50,000	32	150,000 Daily	210	Pneumococcus, spirochetes	1 tap	Yes	Cured. Bloody fluid and persistent local pleural thickening required biopsy revealing only chronic pleuritis.
4 B. B. 26	Empyema, loculated putrid, right	Postlobectomy	5-29-44	7- 5-44	6	20,000	26	None	150	Nonhemolytic streptococcus, bacteroids	2 taps	Yes	Cured
5 E. D. 29	Empyema, loculated, putrid, left	Diffuse suppurative pneumonitis, bilateral	11-20-44	1-18-45	5	25,000	8	None	350	Nonhemolytic streptococcus	1 tap after topical penicillin	No	Cured. Sulfonamides systemically.
6 R. O. 6	Empyema, loculated, right	Pneumonia	1-21-45	3-11-45	4	30,000	7	None	18	Nonhemolytic streptococcus, diphtheroids	1 tap	No	Cured. Sulfonamides systemically. Pneumonia recurred in same RLL, prolonging hospital stay.
7 A. P. 43	Empyema, loculated,left	Postlobectomy	1-31-45	2-25-45	3	20,000	7	150,000 daily for 12 days	180	Pneumococcus, type 5. Nonhemolytic streptococcus Hemophilus influenzae	Never	Yes	Failure. Small bronchopleural fistula, multiloculated, nonsusceptible organisms. Slow and incomplete recovery after surgery.
8 A. S. 35	Empyema, loculated, (2 loculi) right	Pneumonia	2-27-45	3-17-45	1	25,000	1	100,000 daily for 15 days	20	Pneumococcus, type 5	1 tap only	No	Cured. One other unsuccessful tap. Dramatic response. Multilocular.
9 F. H. 40	Empyema, loculated, right	Subphrenic abscess. Appendectomy 6 mos. before	3-28-45	4-17-45	6	40,000 first 20,000 thereafter	15	None	350	Nonhemolytic streptococcus	3 taps	Yes	Cured. Has chronic cough, possibly from bronchiectasis
10 H. R. 30	Empyema, loculated, (2 loculi) right	?	6- 5-45	7-19-45	13	50,000	13	240,000 daily for 20 days	550	Hemolytic streptococcus nonhemolytic, streptococcus, aerobic and anaerobic	Never	No	Never sterilized. Poorly communicating secondary loculus. Rapid recovery after surgical drainage.

TABLE I.—SUMMARY OF CASES—Continued

Case Initials Age	Diagnosis	Etiology	Admitted	Discharged	No. taps	Units of penicillin instilled	Days treated	Units of systemic penicillin	Size of cavity cc.	Bacteriology	Sterile after	Broncho-pleural fistula	Results—Remarks
11 A. A. 64	Empyema, loculated, putrid, right	Bronchiectasis, bilateral	7-19-45	8-26-45	4	10,000	7	100,000 15 days 300,000 17 days	40	No growth	?	No	Cured of empyema. Follow-up 15 months later: under conservative management of bilateral bronchiectasis
12 M. L. 20	Empyema, loculated, putrid, right	Post-lobectomy	8-22-45	9-11-45	4	100,000 first 2 taps 50,000 last 2 taps	4	240,000 daily for 21 days	180	Anaerobic, nonhemolytic streptococcus	2 taps	No	Cured. Sulfonamides systemically first 2 days
13 J. W. 29	Empyema, loculated, putrid, left	Post-lobectomy	9- 7-45	10- 5-45	16	100,000 50,000 100,000	25	150,000 daily for 21 days	315	Hemolytic Staphylococcus aureus	14 taps	No	Cured. Return to larger dose of penicillin and addition of sulfathiazole required to sterilize
14 B. K. 58	Empyema, interlobar right	Pneumonia	11-21-45	12-22-45	4	25,000 first tap 20,000 other taps	11	100,000 daily for 25 days	20	Hemolytic streptococcus, nonhemolytic streptococcus	No negative cultures reported	No	Cured. Penicillin inhalations for 25 days also. Follow-up 9 months: no recurrence
15 C. S. 27	Empyema, multiloculated, putrid, left	Post-lobectomy	12- 3-45	5- 8-46	7	50,000 2 taps 50,000 units streptomycin, 4 taps	6	150,000 53 days 350,000 10 days	60	Bacteroids, diptheroids, Hemophilus influenzae	Never	Yes	Failure. Multiloculated cavity. Small amounts of streptomycin locally and sulfadiazine systemically for 11 days. Poor response even after surgery. Cleared cultures of Hemophilus influenzae without clinical improvement.
16 J. A. 16	Empyema, loculated, left	Pneumonia, pneumonitis?	2- 2-46	2-17-46	5	100,000	6	200,000 daily for 14 days	100	No growth. Pathology showed empyema	1 tap	Yes	Cured
17 W. D. 46	Empyema, loculated, putrid, left	Post-pneumonic	4- 6-46	5-13-46	13	200,000 first tap 100,000 thereafter	33	None	1200	Hemolytic streptococcus	1 tap	Yes	Cured. Had been treated by systemic penicillin and thoracenteses for 9 weeks before admission. Follow-up 3 months; patient well and working
18 W. A. 56	Empyema, loculated, left	Carcinoma, pulmonary	5-26-46	7- 9-46	6	100,000	11	240,000 daily for 36 days	70	Pneumococcus	1 tap	No	Cured of empyema. Pneumonectomy done on 6-24-46 without postoperative infection. Treated by systemic penicillin and sulfonamides before
19 M. H. 61	Empyema, loculated, left	Bronchiectasis	7-14-46	8-16-46	13	100,000 first 6 taps 50,000 thereafter	23	300,000 daily for 34 days	500	No growth	?	Yes	Cured
20 I. R. 56	Empyema, loculated, putrid, right	?	8-16-46 10-29-46	9- 6-46 11-30-46	3	200,000 twice	?	240,000 daily for 33 days (I. M.)	90	Anaerobic, nonhemolytic streptococcus	Never	No	Failure. Uncertain, irregular treatment. Surgical drainage at exploration.

with a No. 20 gauge needle. Then insert a No. 14 or No. 15 gauge needle and use a 30 cubic centimeter syringe with a two-way stopcock as the best means of aspirating the fluid. If the pus is thin, use a modified aspirator devoid of the little Potain valves which are useless and are often completely stuck or partially blocked by rust or cooked exudate. It is important to aspirate all the pus possible; do not be satisfied with less than appears to be present from the physical signs and roentgenograms. It is usually impossible to get all of the pus, since some is present below the level of the needle; this pus can be diluted and largely evacuated by lavaging with normal saline or azochloramide in 1:3300 aqueous solution. In the presence of thick pus which taxes one's ingenuity, particularly if there are fibrinous clots, with movement or rotation of the needle during release of suction, reinstill a few cubic centimeters to blow out fibrinous material, lavage, and instill azochloramide; this procedure usually overcomes this difficulty. The adequate removal of thick pus is one of the greatest difficulties with this method. For the first 3 or 4 days maintain separation of pleural surfaces by pneumothorax or by volume of fluid reinstilled to allow sterilization and to avoid development of multiple loculation if not already present.

2. When the cavity is emptied as thoroughly as possible, instill 100,000 units of penicillin, 1 gram of streptomycin or 2 to 4 grams of sulfonamide alone or combined, depending on susceptibility tests, in appropriate amount of saline, usually 25 to 50 cubic centimeters, plus additional air, if the capacity of the cavity is above 200 cubic centimeters, to maintain separation of the walls.

3. Determine that the organism is susceptible to one of the available agents, but continue the treatment until this is determined. If the bacteria are not susceptible to one of the agents available, surgical drainage should be instituted without further delay.

4. Repeat procedure daily until cultures are sterile or nonsusceptibility is established.

5. As soon as cultures are sterile, obliterate the space as rapidly as possible, removing all liquid and gas, but continue to instill 50,000 to 100,000 units of penicillin or appropriate amounts of other agents in small volume, as low as 1 cubic centimeter with each aspiration. Aspiration is continued every other day until no more fluid can be obtained and frequent roentgen-ray check-up reveals no further evidence of pleural cavity, when taps may be discontinued.

6. Check-up by roentgen-ray in 2 weeks and again in 4 weeks, using exploratory aspiration if roentgenogram indicates suspicion of persisting fluid or cavity.

7. Give the appropriate antibiotic (or chemotherapeutic agent) systemically. Penicillin is administered in 12 doses intramuscularly 2 hours apart, totaling 240,000 units per day or more, starting this at the beginning of the topical application. Streptomycin is given in similar fashion, totaling 3,000,000 units per day. Sulfonamides are better given by mouth in the usual way.

8. If it is impossible to empty the cavity, if susceptibility cannot be established or if satisfactory technique fails to relieve the condition within 10 to 14 days, institute drainage.

PREVIOUS REPORTS

It is notable that the literature on this method is mostly adverse. A critical analysis, however, reveals that many of the reports are of small groups, that patients have been tapped irregularly and infrequently, that pus has been allowed to remain in the pleura even though sterilized, or that surgical drainage has been instituted at once because of thick pus or the presence of bronchopleural fistula. Consider the article by that excellent surgeon, Brian Blades, in collaboration with Hamilton and Dugan in which they report 24 cases in which patients were treated at various Army posts. Of these, the record indicates that dosage was inadequate in amount or time or both in 9 and that sterile fluid, which might have been removed, was present in 7, a total of 16 which might have been successful. In only 3 patients were nonsusceptible organisms present, and in 3 others there was cure without operation. They note that pus became thicker as time went on, although we have observed the opposite in our cases, in that the pus becomes thinner from the first tap, provided adequate removal is obtained. The reference to thick

pus and the inefficacy of this method occur in other reports, including those of Roberts, Tubbs, and Bates from England, and Poppe, who also feel that bronchopleural fistula is a contraindication. Poppe reports a recurrence rate of 53 per cent and quoted Butler, Perry and Valentine as having a 28 per cent recurrence rate. He feels that treatment in this fashion greatly prolongs morbidity and that this is another reason it is not justified. We have seen no recurrences with the technique described above and have noted a great reduction in morbidity. He also feels that pleural thickening is more frequent and more crippling with aspiration therapy than with drainage. Prolonged thickening was noted in only two of our aspiration cases, and has been present in most of our previous drainage cases as well. The thickness appears to be the response to infection and occurs in proportion to the virulence and duration and has been as routinely present in previous patients treated by surgery alone. Follow-up roentgenograms of our patients showed routine disappearance of pleural thickening within a few months in all but the 2 mentioned.

On the other hand, Lockwood, White, and Murphy reported 34 cases of pneumococcus empyema of which 19 were cured in this way with only 10,000 to 25,000 units of penicillin topically. One of these showed Staphylococcus aureus, Streptococcus hemolyticus and pneumococcus. Hirshfeld, Buggs, Abbott, and Pilling seem to have a most rational approach and, although they do not state the number treated and the percentage of success, they cite successful and unsuccessful cases, and they, as well as we, emphasize the need for maintaining the principles of treatment of empyema with this method as with any other. Brown and associates, in reporting 24 cases of their own and 236 compiled from the literature, state that in 144 patients treated with penicillin locally or systemically or both, 92.3 per cent were cured, 2.6 per cent became chronic and 5.1 per cent died. In 104 patients treated by penicillin and surgery, 90 per cent were cured, 3.8 per cent became chronic, and 5.8 per cent died. They, too, call attention to the small number of injections in many cases, often only one or two injections being given and frequently doses as low as 10,000 units being used.

Much of the criticism of this method may stem from analyses and compilations of cases in which patients were treated by physicians not surgically trained, although certainly some of it represents poor results in the hands of good surgeons.

CONTRAINDICATIONS

It is quite probable that in certain cases with pus which is too thick for evacuation by large needle and persistent effort, with organisms which are not susceptible or with the presence of large bronchopleural fistula which prevents proper lavage or retention of the antibiotic in the cavity, surgery would be necessary, but these should be infrequent. The contraindications as they appear to us are:

1. Inability to evacuate the cavity.
2. Nonsusceptible organisms.
3. Inability to maintain antibiotic fluid in the cavity, as in large bronchopleural fistulas.
4. Multiple loculi; although theoretically even this might be overcome by tapping each loculus, such tapping generally would not be feasible.
5. Recurrence.

CASE REPORTS

CASE 1. M. S., female, age 47, was admitted to the hospital January 2, 1944; discharged February 4, 1944. Diagnosis: empyema, diffuse, right, pneumococcic, postpneumonic.

This patient's illness dates from December 25, 1943. She developed cough, fever, and labored breathing and was treated at home as pneumonia. The cough became more severe and productive and she was referred to the hospital. She presented signs of fluid over the right lower chest posteriorly; her temperature was 102.2 degrees, and she appeared quite toxic. The roentgen-ray examination January 3, 1944, revealed a large pleural collection within the right chest with displacement of the mediastinum to the left. February 11, 1944, the roentgenogram revealed complete obliteration of the empyema cavity.

The patient was tapped on January 3, 1944, and 900 cubic centimeters of greenish-yellow fluid were removed. She was started on sulfonamides systemically. No penicillin was instilled on the first tap. After surgical consultation on January 13, 1944, taps were done almost daily, on January 14, 16, 17, 18, 19, 20, 22 and 29, 10,000 units of penicillin being instilled at each tap. At the time of the last tap, the size of the cavity was approximately 35 cubic centi-

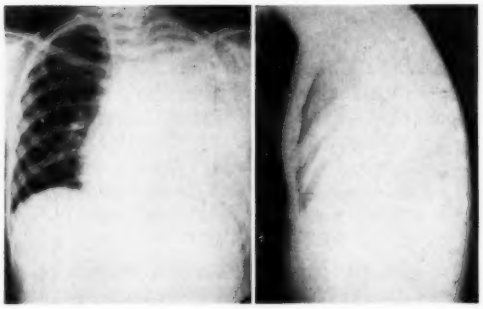

Fig. 1. Case 2. A. R., massive empyema on left demonstrated on January 10, 1944, the day after admission.

meters, and only serosanguineous fluid was withdrawn. Pneumococci were found in the specimens until January 16, 1944. Following this, on three subsequent taps, gram-positive diplococci were seen in smears, but there was no growth. Following these taps, each specimen was sterile and showed no organisms. The patient received no systemic penicillin. Her systemic sulfonamides consisted of 6 grams per day from January 2 to 11, 1944, inclusive, none being given during empyema treatment.

Follow-up: The most recent examination of this patient was on December 12, 1946. She had had no further cough, dyspnea, or other respiratory symptoms and had gained 18 pounds in weight. There is no recent check-up roentgenogram.

CASE 2. A. R., female, age 9, was admitted to the hospital January 9, 1944; discharged February 29, 1944. Diagnosis: empyema, massive, left, pneumococcic.

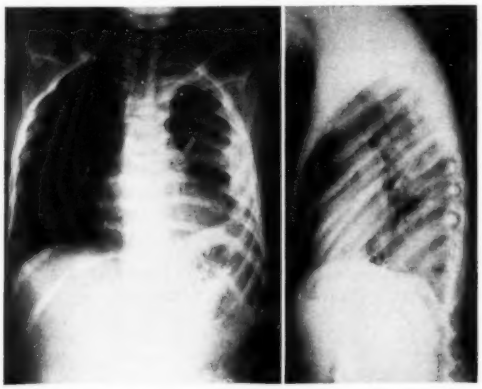

Fig. 2. Case 2. A. R., February 25, 1944, approximately 7 weeks after admission and 3 weeks after last successful tap. Marked pleural thickening and the usual hitching up of diaphragm after empyema treated by any method appear, but no cavity is demonstrable.

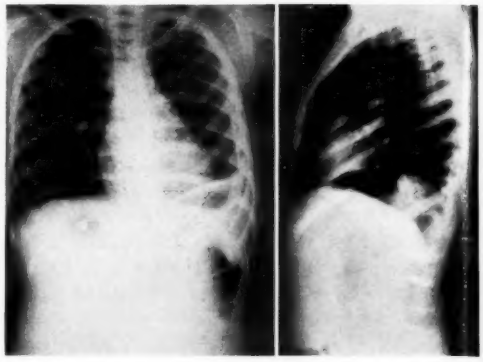

Fig. 3. Case 2. A. R., on March 30, 1944, 11 weeks after admission and 8 weeks after last successful tap. Pleural thickening greatly reduced. Diaphragm still elevated.

Cough, fever, weakness, and toxemia for the 3 weeks prior to admission beginning insidiously with an upper respiratory infection. Patient presented a marked pallor, with signs of fluid in left chest and cervical adenopathy. On January 10, 1944, roentgenogram revealed massive left pleural effusion with the condition of the underlying lung indeterminate.

The patient was first tapped on January 11, 1944, and thick pus culturing pneumococcus, type 5, was revealed. Beginning on January 13, 1944, or 4 days after admission, aspirations were done daily with reinstillation of 12,500 units of penicillin. Aspirations were rather small, ranging from 1½ to 90 cubic centimeters, and cultures continued to be positive. On January 19, 1944, a determined effort removed 360 cubic centimeters, and from this point on progress was rapid. Cultures became sterile from January 24, 1944, and for 10 subsequent studies, and only small amounts of bloody, serous fluid could be obtained thereafter. From this point on her temperature rapidly returned to normal and she improved clinically. The last successful thoracentesis was February 3, 1944, approximately 10 days after the thorough aspiration, and only a few cubic centimeters of serous fluid were removed. On discharge, the patient showed complete obliteration of the empyema cavity with some residual pleural thickening. She was asymptomatic, her leucocytosis had disappeared, her sedimentation rate was normal, and physical signs in the chest were practically normal.

Follow-up: The patient was seen up to 34 months after discharge, and both clinical and roentgen-ray examinations were entirely normal (see Figs. 1 to 4).

CASE 3. A. S., male, age 55, was admitted to the hospital March 10, 1944; discharged April 12, 1944. Diagnosis: (1) empyema, loculated, left; (2) fistula, bronchopleural; (3) abscess, subcutaneous.

Five months before admission, a diagnosis of left-sided pleurisy and pneumonia had been made. Since this acute episode the patient had improved but had

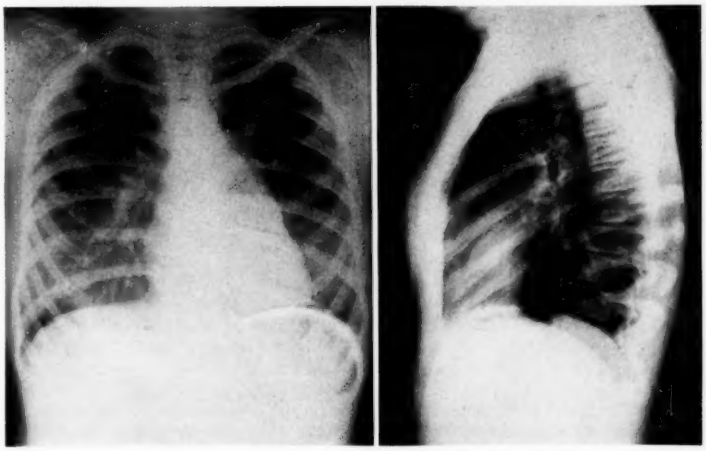

Fig. 4. Case 2. A. R., on November 12, 1946, 35 months after treatment showing normal lung fields and pleura. Diaphragm has returned to normal position and activity.

never felt well, and had continued to have pain in his left chest with some dyspnea and a persistent, productive cough. The cough became worse when he lay on his right side, and the sputum was profuse but not foul. He had lost some 10 pounds in weight. In the last 2 weeks he had noted a hard, red swelling over the left chest wall anteriorly, which had increased in size but had not drained. Examination disclosed enlarged, left supraclavicular nodes, lagging and dullness over the entire left chest with suppression of breath and voice sounds. In the anterior axillary line at the sixth rib there was a red, tender mass about 5 centimeters in diameter which was attached to underlying muscles and costal cage. Roentgenograms revealed a hydropneumothorax on the left which was loculated in the lower lateral portion from the diaphragm to the third rib. There was some infiltration of the left lower lobe, suggesting pneumonitis, and accentuation of the lung markings in the right lower lobe, suggesting possible bronchiectasis.

Aspiration on March 11, 1944, 2 days after admission, obtained 210 cubic centimeters of bloody, thick, putrid pus which on culture, grew pneumococcus and spirochetes. The red mass was drained and found to be a local abscess, not communicating with the pleura, which showed a hemolytic Staphylococcus aureus. Aspirations were done on March 12, 13, 14, 15, and 17, at which times penicillin, 50,000 units, was instilled, except on the 15th when an unsuccessful tap was encountered. Pus on March 12, 1944, was nonodorous and that obtained on March 13, 1944 was sterile. There was no other positive culture on any subsequent tap. On March 24, roentgenogram showed a reaccumulation of fluid, and he was aspirated on this date and on March 25, but on March 27, and March 29, the taps were unsuccessful. However, they were again successful on April 1, 5, 6, 8, 10 and 12. On the last tap only 5 cubic centimeters of thin, very slightly bloody fluid were removed. Penicillin was given intramuscularly from March 10 to 18, 1944 at the rate of 150,000 units per day. He was discharged on April 12, 1944, with a healed wound at the site of the drained abscess and without respiratory symptoms. Roentgenogram showed obliteration of the pleural cavity, but continued to show a localized area of pleural thickening. This continued without much change for 6 weeks, which increased our fear of an underlying tumor which had been suggested by the bloody fluid. For this reason a biopsy of the pleura was done on May 29, 1944, but only chronic pleuritis was found.

Follow-up: On September 24, 1945, approximately 17 months after discharge, the patient had remained free of cough, expectoration, and fever, and roentgenogram revealed only slight residual pleural thickening with blunting of the left costophrenic sulcus and elevation of the diaphragm.

CASE 4. B. B., female, age 26, was admitted to hospital, May 29, 1944; discharged July 5, 1944. Diagnosis: (1) bronchiectasis, right lower lobe; (2) empyema, loculated, right, putrid, postlobectomy; (3) fistula, bronchopleural.

Bronchiectasis followed the inhalation of grass head at the age of 9 years. Cough and expectoration had been present since and hemoptysis and malodorous sputum were recently noted. Examination revealed dullness of right base, otherwise negative. Roentgenogram June 9, 1944 (first postoperative x-ray) showed fluid present along the right lateral chest wall and a fluid level of the fifth interspace in the posterior axillary line. June 24, 1944: the roentgen-ray appearance of the chest improved considerably in the past 11 days, resulting in disappear-

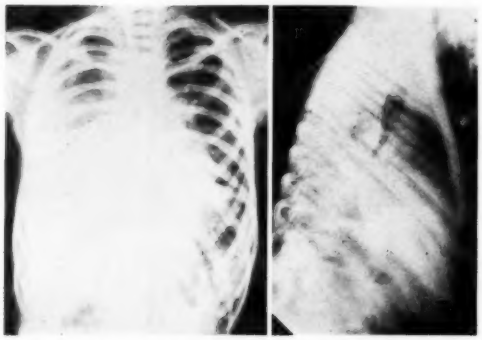

Fig. 5. Case 6. R. O., on January 30, 1945, fluid posteriorly and laterally following right lower lobe pneumonia.

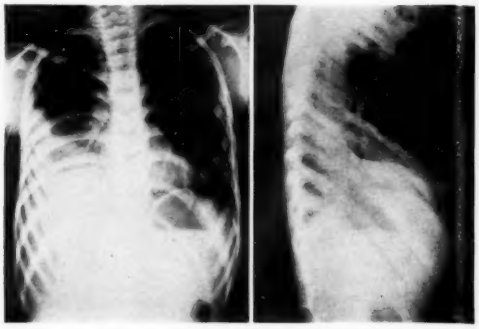

Fig. 6. Case 6. R. O., 8 days after last successful thoracentesis.

ance of fluid loculation in the posteromedial aspect of the chest. No undrained fluid collections were evident.

Following lobectomy on June 5, 1944 for right lower lobe bronchiectasis done without chemotherapeutic protection, the temperature remained elevated, and roentgenograms showed pockets of fluid. On June 13, 1944, thoracentesis was done, and 150 cubic centimeters of bloody, foul-smelling fluid were removed and 20,000 units of penicillin instilled. Culture of this material showed Bacillus pyocyaneus, many nonhemolytic streptococci, and a few bacteroids. On June 15, 1944, another tap was done; 150 cubic centimeters of very slightly odorous fluid were removed and 20,000 units of penicillin instilled. Culture was again positive. No subsequent cultures could be obtained. On June 17, 1944, the procedure was repeated, large amounts of air removed and 20,000 units of penicillin instilled. On June 19, 1944, thoracentesis was again done, but no penicillin instilled. On June 21, 1944, thoracentesis was done, removing much air but no fluid, and 20,000 units of penicillin were instilled. On June 24, 1944, 20,000 units of penicillin were instilled. Air was still present at this time. No other thoracenteses were done. On July 5, 1944, the patient was discharged with a normal temperature. At that time there was practically no sputum. Morbidity after operation had continued with a temperature of from 101 to 103 degrees until the tenth postoperative day when the second thoracentesis was done. The temperature then dropped rapidly to normal and remained so until discharge. No sulfonamides were given.

Follow-up: Following discharge the patient received bi-weekly instillations of penicillin by bronchoscope because of a bronchial fistula and fear of re-contamination; however, dosage was not noted. On September 28, 1944, she was seen by us and was absolutely asymptomatic. Roentgenograms taken in Texas in November, 1945, showed no residual cavity or pleural thickening. Two communications received from the patient's family physician 2 years following the procedure stated that she was completely asymptomatic and roentgenograms of the chest were entirely negative.

Case 5. E. D., male, age 29, was admitted to the hospital November 20, 1944; discharged January 18, 1945. Diagnosis: (1) pulmonary suppuration, bilateral, diffuse; (2) empyema, loculated, left.

In 1943, the patient had 13 teeth extracted, following which he developed fever, productive cough, nausea, vomiting, and 3 days later he coughed up a portion of tooth. He developed 5 attacks of pneumonitis since this episode, of which 3 were in 1944. He was given a course of sulfonamides on the outside, with no relief. He had marked dyspnea and pain in the left lower chest. Examination revealed dullness to percussion posteriorly over both bases extending up to sixth thoracic. Coarse râles were heard over both bases, and breath sounds were diminished. There were tachycardia, fever, and weight loss. Roentgenograms November 21, 1944, revealed widely disseminated disease in the lungs, probably nontuberculous in character. December 1, 1944, the chest appearance was somewhat worse than on examination 10 days ago. There was an abnormal density in the left lung which had increased in extent and showed confluence. There was fluid collection in the left base. January 1, 1945, marked improvement was noted with only pleural thickening present. No empyema pocket was found.

Systemic penicillin, 100,000 units, was given intramuscularly from November 24 to December 16, 1944, with little improvement. All sputum specimens were negative for tuberculosis. On January 4, 1945, surgical consultation was requested, and a diagnostic left thoracentesis obtained 5 cubic centimeters of foul greenish pus which grew many hemolytic streptococci. On January 5, 1945, a therapeutic tap removed 350 cubic centimeters of similar pus. The cavity was lavaged with saline, and 25,000 units of penicillin in 50 cubic centimeters of saline was instilled. The pus showed the same organisms, but all subsequent cultures were sterile. Thoracenteses were repeated on January 6, 8, 10, and 12, obtaining 90, 40, 25, and 10 cubic centimeters of nonodorous fluid

which became thinner until the last 10 cubic centimeters appeared to be a solution of penicillin in consistency and color. On each occasion, 25,000 units of penicillin were reinstilled. From January 10, 1945, the patient felt much better, gained weight, and was free of his distressing cough. His low-grade fever disappeared permanently after the first instillation of antibiotic. He was discharged on January 18, 1945, markedly improved clinically, and roentgenograms showed similar improvement in the parenchymal disease on the left and in the pleural disease.

Follow-up: Subsequent roentgenograms continued to show bilateral pulmonary disease. The patient was readmitted in November, 1946, with evidence of right-sided pleural thickening and parenchymal fibrosis. However, the left pleural space remained entirely free of infection and has continued so to the present. A right lower lobe lobectomy was performed with resection of a portion of the diaphragm, liver, and parietal pleura for his right-sided pulmonary, pleural, and hepatic disease which resembled actinomycosis but was not proved microscopically.

CASE 6. R. O., male, age 6, was admitted to the hospital January 21, 1945; discharged March 11, 1945. Diagnosis: (1) pneumonia, right lower lobe; (2) empyema, loculated, right, streptococcic.

Fever and cough were present for the 2 weeks prior to admission. He was treated with sulfonamides by his local doctor, with no improvement. He was admitted with a diagnosis of right lower lobe pneumonia. Examination revealed an increased respiratory rate and dullness to percussion posteriorly, in the regions of the right middle and lower lobes. Breath and voice sounds were diminished. An occasional moist râle was heard over the right base. Roentgenogram January 22, 1945, revealed consolidation of the right middle and lower lobes, interpreted as pneumonia. There was a question of fluid in the right pleural space. January 30, 1945, pneumonia had resolved. There was appreciable fluid collection in the right pleural space which appeared to be loculated. March 10, 1945, roentgenogram showed no evidence of pleural disease.

The patient was placed on sulfonamides on admission, with immediate improvement. A dosage of 3 grams daily was given from January 21, 1945, to February 10, 1945. His temperature returned to normal the third day after admission. One week after evident resolution of pneumonia, the patient developed signs of fluid in the right chest and temperature elevation. A diagnosis of empyema was made. Thoracenteses were done on January 29, 30, and 31, and February 3. The initial tap produced 18 cubic centimeters. Bacteriological examination revealed an anaerobic, nonhemolytic streptococcus on January 29, 1945. Thereafter all fluid was sterile. The first three thoracenteses were productive. At the last tap no fluid could be obtained. Penicillin, 30,000 units, was instilled at each tap. He was begun on 100,000 units of penicillin intramuscularly daily on January 30, 1945, which was continued until February 21, 1945.

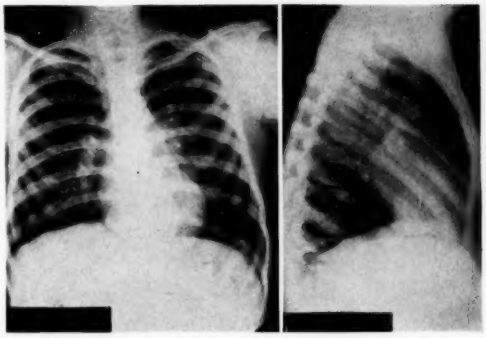

Fig. 7. Case 6. R. O., 19 months after treatment. Entirely well.

Follow-up: Since discharge the patient has had no recurrence of chest symptoms. He was seen in August, 1946, at which time he had no pulmonary complaints. Examination of the chest was entirely negative, and check-up roentgenograms showed no pathologic change and no evidence of pleural disease.

CASE 7. A. P., female, age 43, was admitted to hospital January 31, 1945; discharged April 25, 1945. Diagnosis: (1) bronchiectasis; (2) empyema, posterior, left; (3) fistula, bronchopleural.

The patient had a left lower lobectomy 6 months prior to this admission. She had a known bilateral bronchiectasis and a history of asthma. On January 29, 1945, she noted upper respiratory infection with chills, fever, and pain in the left lower chest and abdomen. A productive cough began on the date of admission. Examination revealed an acutely ill woman. Her respirations were 36, pulse 144, and temperature 103 degrees. There was a lag in the left chest with dullness at the left base posteriorly and signs of fluid in this region. Roentgenogram, February 1, 1945 revealed a large hydropneumothorax in the left chest with a broad fluid level. The left upper lobe was collapsed. April 10, 1945, roentgenogram revealed thickened pleura in the left chest, but no air or fluid pocket.

On admission the patient was markedly debilitated and showed a morbidity which persisted throughout her hospital stay. Her temperature spiked as high as 102 to 103 degrees daily. The first two taps showed no purulent material and revealed no organisms. The first measurable amount of fluid was obtained on February 1, 1945, when 10 to 15 cubic centimeters were removed with large amounts of air. Culture on this material was sterile. The tap was repeated on February 8, 1945, but no fluid was obtained. On February 19, 1945, 60 cubic centimeters of malodorous pus were withdrawn, and 16,000 units of penicillin instilled. Bacteriological examination revealed pneumococci, type 5. On February 21, 1945, 100 cubic centimeters of odorous pus were removed, and 20,000 units of penicillin instilled. On February 23, 1945, 180 cubic centimeters of thick,

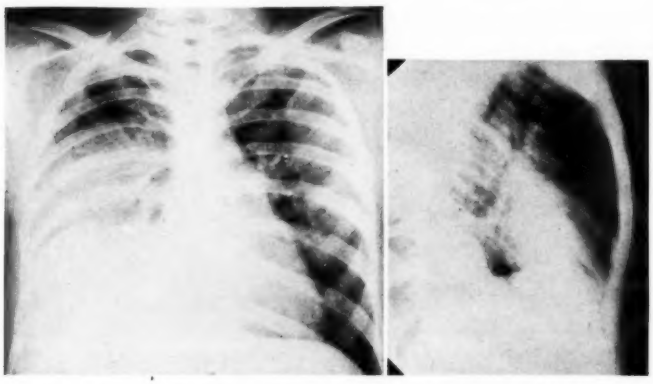

Fig. 8. Case 10. H. R., on June 6, 1945, admission films showing loculated empyema, right base posteriorly.

brown, nonodorous fluid were removed, and 20,000 units of penicillin instilled. Failure to respond to this sporadic treatment and the scarcity of penicillin made us elect surgery. On February 26, 1945, the cavity was opened and drained. The empyema fluid never became sterile on the infrequent penicillin instillations. The left upper lobe remained atelectatic until controlled drainage with suction was placed in the left pleural space. On April 11, 1945, a small cavity near the apex was discovered, and this was tapped on April 11 and 12, 20,000 units of penicillin being instilled each time. The material obtained from this pocket was sterile. The underlying lung disease probably played a large factor in this patient's continued morbidity, and she was discharged at her own insistence running a moderately septic temperature.

Follow-up: The patient was seen again in June, 1945, on a readmission, at which time she showed marked debility and edema due to protein deficiency. Roentgenogram at this time showed a fluid level in a new location in the apical portion of the left chest which was definitely localized in the pleural space. There was marked parenchymal adjacent lung disease. The patient was also still draining through the drainage opening in the fifth left rib bed made on the previous admission. She has been seen since in the out-patient department and continues to get along with difficulty, having dyspnea and asthmatic symptoms, although less than before lobectomy, and slight drainage through the thoracostomy wound.

This patient was subjected to lobectomy originally after considerable thought and discussion in the chest conference. The bronchiectasic left lower lobe was removed in the belief that her severe asthma was produced by bacterial allergy from the bronchiectatic focus. She was improved, and although she still has asthma it is much less severe.

Infection in the pleura was produced by a respiratory infection 6 months following lobectomy. There was difficulty in locating the pus. There were multiple pockets, the pus was malodorous, although only pneumococci could be grown from one of the pockets, and penicillin was scarce. She was therefore drained 27 days after admission and this, too, was not very satisfactory although adequate access was obtained by rib resection. She refuses additional surgery and we agree with her.

Case 8. A. S., male, age 35, was admitted to the hospital February 27, 1945; discharged March 17, 1945. Diagnosis: empyema, loculated, right, pneumococcic, postpneumonic.

The patient was well until January, 1945, when he developed what was diagnosed as lobar pneumonia on the right. He was treated with sulfonamides at home, and his fever disappeared. A few weeks later he noted a temperature elevation each afternoon. He lost 34 pounds. Two weeks before admission he developed diarrhea, pain in the right chest, a productive cough and dyspnea. Examination revealed flatness at the right base posteriorly. Crackling râles were heard at both bases posteriorly. Breath and voice sounds were diminished on the right. There was slight abdominal distention. Roentgenogram February 28, 1945 revealed 2 fluid loculations in the right lower portion of the right pleural space, one lateral and one posterior. There was abnormal stringy density present in the left lower lobe. Roentgenogram March 12, 1945, showed that no significant change had occurred during the past week. At the time of discharge x-ray examination showed only a small residual cavity in the right lower pleural space.

The first tap was done on March 5, 1945, and 20 cubic centimeters of frank, nonodorous pus were re-

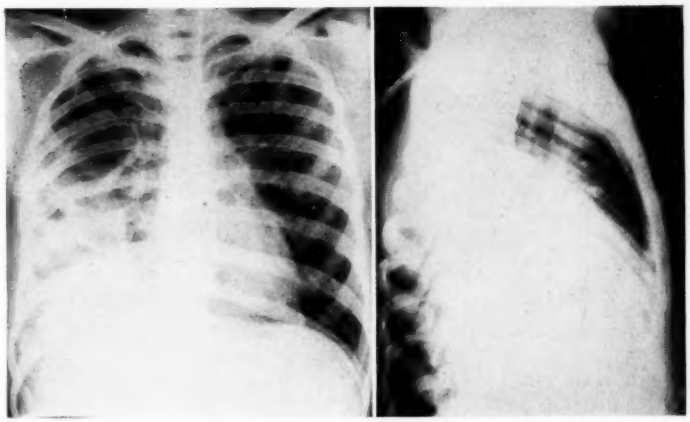

Fig. 9. Case 10. H. R., on June 18, 1945, after 12 days' treatment showing multilocular cavity. Still had positive cultures. Drainage instituted the following day.

moved, and 25,000 units of penicillin were instilled. The pus was cultured and showed pneumococci, type 5. Patient's temperature immediately returned to normal, and his clinical improvement was dramatic. No other taps were successful in obtaining air or fluid. The patient received no systemic sulfa therapy. He received systemic penicillin from March 2, 1945 to March 17, 1945, 100,000 units daily.

Follow-up: This patient was seen by his family physician until 1 year ago, at which time he had had no recurrence of symptoms, was perfectly well, and was working. We had an opportunity to examine him in January, 1947. He had no recurrence of symptoms at that time, and a roentgenogram taken then was negative.

It is of interest to note a cure in this case without obliteration of the multiloculated cavity at the time of discharge. We consider it an error to take such risk.

CASE 9. F. H., male, age 40, was admitted to the hospital March 28, 1945; discharged April 17, 1945. Diagnosis: (1) empyema, loculated, right; (2) fistula, bronchopleural.

In April, 1944, the patient developed a productive cough, dyspnea on exertion, pain in the right chest, ankle edema, and easy fatigue. In September, 1944, he had an appendectomy followed by a subdiaphragmatic abscess which was drained in October, 1944. He states that his chest was also drained shortly thereafter but only one scar is visible. The cough has persisted since. Examination revealed dullness in the right chest posteriorly up to the seventh rib with decreased breath sounds. Roentgenogram March 28, 1945, showed a large hydropneumothorax in the right base, extending to about the seventh rib posteriorly. May 3, 1945, roentgenogram showed no fluid in the right base since the examination 3 weeks previously. Pneumonitis in the right lower lobe was clearing.

The patient had occasional morbidity with temperature reaching 100 degrees as on the day of admission. On March 29, 1945, the day after admission, thoracentesis was done and 350 cubic centimeters of fluid were removed which grew anaerobic nonhemolytic streptococci. The fluid was nonodorous. It was repeated on March 31 and April 6, 10, 11, and 12. Penicillin, 40,000 units, was instilled on the first tap and 20,000 units on each of the following taps. Cultures were sterile after the third tap on April 6, 1945. Morbidity disappeared rapidly, and the patient improved markedly. His sputum volume had dropped from 300 cubic centimeters to zero in 6 days. No sulfonamides or systemic penicillin were given.

Follow-up: Unfortunately, we have no follow-up roentgenograms of this patient; however, we have had two communications from him in which he stated he had numerous lower respiratory infections, probably on the basis of his residual parenchymal disease. He has had no episodes which resemble his previous attacks and is fever free and symptom free for long periods of time between these infectious episodes. He will not return for further study but probably has right lower lobe bronchiectasis.

CASE 10. H. R., male, age 30, was admitted to the hospital June 5, 1945; discharged July 19, 1945. Diagnosis: empyema, loculated, right.

The patient was well until 14 days before admission, at which time he began to feel weak and listless and, on May 26, 1945, he developed nausea. The symptoms increased, and he developed a dry, nonproductive cough and had a gradual increase in temperature, which on admission was 104 degrees. Examination revealed limitation of expansion of right chest, dullness from sixth thoracic down in the right axillary region with impairment of voice and breath

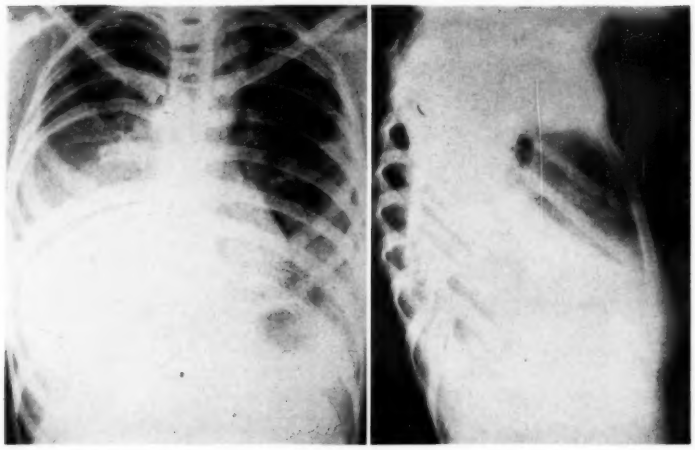

Fig. 10. Case 12. M. L., on August 22, 1945, fluid in right pleural space 1 month after right lower lobectomy for bronchiectasis.

sounds. Crackling râles were also heard in this area. Roentgenogram, June 6, 1945, revealed a large fluid collection in the right pleural space, possible empyema which appeared to be loculated. On June 18, 1945, roentgenogram revealed an empyema loculus 8 by 4 by 4 centimeters. There was also another loculated collection at the right base more posteriorly situated (Figs. 8 and 9).

His temperature on admission was 104 degrees and his pulse 140. He was given sodium sulfadiazine intravenously for 2 days and sulfadiazine orally for 4 days. Penicillin, 230,000 units daily, was given from June 6 to 25, 1945. He received thoracenteses daily from June 6 to 18, 1945 with evacuation of all available pus and instillation of 50,000 units of penicillin. On the first tap 550 cubic centimeters of pus were removed. On aerobic and anaerobic culture the pus showed hemolytic and nonhemolytic streptococci. These were present in all specimens obtained. The patient showed slight improvement after the first few thoracenteses, but improvement was slow and his temperature never reached normal. On June 18, 1945, it was decided to do an open drainage because of continued positive cultures, and at this time a second partially drained loculus over the diaphragm was discovered. The patient improved rapidly after drainage and was discharged 1 month later.

Follow-up: The patient was seen in the hospital on September 27, 1945, with no recurrence of symptoms. Follow-up films showed complete resolution of the empyema and only minimal pleural thickening. Letters up to April 1, 1946 stated that he had had no recurrence of symptoms.

Case 11. A. A., male, age 64, was admitted to the hospital July 19, 1945; discharged August 26, 1945. Diagnosis: (1) bronchiectasis; (2) empyema, loculated, right, putrid.

The patient was well until October, 1941, when he developed pneumonia from which he recovered, but 4½ months later he again developed pneumonia from which he recovered after a long period of convalescence. He stated that his temperature never returned to normal. He was admitted to a hospital on July 22, 1942, and a diagnosis of left lower lobe bronchiectasis was made. His symptoms, which had continued until his admission on July 19, 1945, were of weakness, poor appetite, and fever. Examination revealed dullness to percussion in the right base posteriorly with crackling râles in both bases; a scar from previous drainage on the left; tachycardia with questionable cardiac enlargement. Roentgenograms on July 20, 1945, showed abnormal density in the right lower hemithorax on the basis of marked pleural disease. Empyema was not suggested by these films. August 7, 1945, films revealed a well demarcated empyema loculus in the right base in the midclavicular line; on August 22, 1945, the pleural parenchymal disease in the right base appeared to be stationary and only the possibility of fluid in the old empyema loculus previously described was noted.

On admission, the patient was markedly debilitated with a septic type of temperature reaching 103 degrees daily. On July 19, 1945, he was placed on penicillin systemically, 100,000 units intramuscularly being given daily, and this was increased to 300,000 units August 2, 1945. On August 7, 1945, a loculated empyema was discovered and treatment by aspiration and instillation of penicillin was begun. Aspiration on August 8, 1945 obtained 40 cubic centimeters of grayish-yellow, putrid pus, and 100,000 units of penicillin were instilled. This pus never showed any organisms on smear or culture. On August 9, 1945, a small amount of thick pus was aspirated, the cavity was irrigated, and 100,000 units

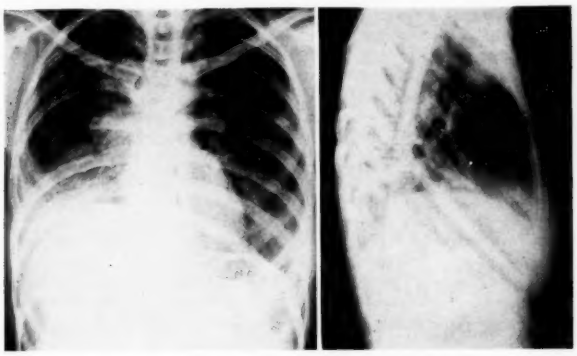

Fig. 11. Case 12. M. L., on September 6, 1945, 15 days after admission and 12 days after last tap. Follow-up 4 months later revealed no symptoms and roentgenogram showed minimal pleural thickening.

of penicillin instilled. On August 12 and 13, 1945, small amounts of pus were obtained, and 50,000 units of penicillin instilled on each of these days. Thoracentesis was again attempted on August 14, 15 and 16, but no fluid could be obtained and no penicillin was instilled. Morbidity dropped sharply after the first instillation of penicillin, his temperature reaching 98.3 degrees on August 9, 1945, and remaining normal from that day until discharge. The original pus was definitely putrid.

Follow-up: This patient was seen by us on November 12, 1946, 15 months after discharge, and had no complaints, except the persistent, chronic cough. He was getting regular bronchoscopic aspirations for his bronchial disease. His appetite was good, and, on physical examination, he was well nourished. There was slight impairment of resonance in the left base and impairment of breath and voice sounds. Tactile fremitus was increased in the same area, and a few moist râles were also present at the right base. Physical examination was otherwise essentially negative. Roentgenograms taken on November 12, 1946 showed evidence of bilateral bronchiectasis. The pleural disease remained minimal.

CASE 12. M. L., female, age 20, was admitted to the hospital, August 22, 1945; discharged September 11, 1945. Diagnosis: (1) bronchiectasis, right lower lobe; (2) empyema, loculated, putrid, right, postlobectomy.

The patient had a right lower lobe lobectomy for bronchiectasis in July, 1945. Her postoperative course was relatively uneventful; however, at the time of discharge a small fluid collection was noted on the right side. At this time the fluid aspirated was sterile. One week before the present admission, the patient developed fever, chills, nausea, vomiting, and productive, foul-smelling cough. She was readmitted for further study. Examination revealed a right-sided scar and slight deformity of a missing rib. There were fine râles posteriorly on the right. Vocal resonance was increased in the interscapular region down to the seventh interspace but from here to the 12th rib it was decreased. Anteriorly over the right lung, fine râles were heard. There was marked tenderness over the lower right chest posteriorly. Roentgenograms August 22, 1945 revealed a large empyema on the right. On September 6, 1945 the films showed marked improvement, and much of the abnormal density in the right lower lung field had disappeared. Considerable pleural thickening was still apparent along the right lateral chest wall, but no fluid was present at this time.

The patient was tapped on the day of admission, August 22, 1945, and 180 cubic centimeters of very thick, foul, bloody pus were removed with no air. Penicillin, 100,000 units, was placed in the cavity. The tap was repeated on August 23, 24 and 25, 1945. The amount of penicillin instilled was 100,000 units on the first two taps and 50,000 units on the last two taps. Systemic penicillin, 240,000 units intramuscularly daily, was given from August 22 to September 11, 1945. Bacteriology showed anaerobic, nonhemolytic streptococcus present in the empyema fluid. Cultures were sterile after the second tap.

Follow-up: This patient was last seen in January, 1946, 4 months after discharge, at which time there was no evidence of recurrence of the empyema. The patient had no complaints, and roentgenogram at this time showed the chest to be clear with a minimal amount of pleural thickening at the right base. The succeeding year brought no further symptoms.

CASE 13. J. W., male, age 29, was admitted to the hospital September 7, 1945; discharged October 5, 1945. Diagnosis: empyema, loculated, left, putrid, postlobectomy.

Approximately 6 weeks before admission the patient had a left lower lobe and segmental left upper lobe lobectomy for bronchiectasis. His postoperative course was uneventful. A hydropneumothorax present on the left was aspirated on numerous occasions, and all of the fluid was found to be sterile. He was discharged about 1 month previous to this

admission. Shortly thereafter he developed a productive cough and recurring bouts of fever. Examination showed a patient of poor nutrition, of pale color and with some degree of exophthalmos. His chest revealed a healed scar of the previous left lower lobe lobectomy. Over the left lower chest the breath and voice sounds were decreased. Moist râles and wheezing were heard over the rest of the left chest. The right chest was clear. Roentgenograms September 8, 1945, revealed a large pleural collection in the left chest posteriorly with evidence of fluid extending from the diaphragm to the seventh interspace. October 4, 1945 (discharge film) showed residual pleural thickening and a small amount of fluid.

The patient was begun on systemic penicillin on September 9, 1945 and continued on it until September 29, 1945, receiving 150,000 units daily intramuscularly. His temperature on admission was 102.2 degrees, with an increased pulse and respiratory rate. This increase returned to normal on the first day of penicillin systemic therapy. Thoracentesis was first done on September 10, 1945, 315 cubic centimeters of slightly odorous pus being removed from the left base and 100,000 units of penicillin being instilled. This dosage was repeated on September 11, 1945, and 100,000 units of penicillin were instilled. Aspirations were again done on September 12, 15, 17, 18, 19, 20, 22, and 24, at which time only 50,000 units of penicillin were instilled. Although the size of the cavity was decreasing according to the amount of fluid and air removed, the cultures persistently revealed a hemolytic Staphylococcus aureus throughout all this time. On September 25, 1945, penicillin and 1 gram of sulfathiazole microcrystals were instilled in the chest after aspiration. Taps were continued on September 27, 28, 29 and 30. Sulfathiazole was again instilled on September 29, 1945 and again on October 3, 1945. On the other taps, 100,000 units of penicillin was instilled. The culture became sterile after the tap of September 29, 1945, and remained sterile on September 30, 1945 and October 3, 1945. This organism was found to be only moderately susceptible to penicillin but susceptible to sulfonamides. At the time of discharge, the cavity could not be entered and on the previous tap only 6 cubic centimeters of yellowish, nonodorous, thin fluid were removed. It is of interest to note that this patient's culture remained consistently positive while on penicillin, but rapidly became sterile on two instillations of sulfathiazole.

Follow-up: Since his discharge film, which was not too satisfactory, this patient has had a good follow-up series with no evidence of an empyema cavity. His sputum volume remained approximately the same, but this was attributed to his slight contralateral bronchiectasis. On January 16, 1946, when he was readmitted for removal of nasal polyps, the chest was clear and roentgenogram showed no evidence of recurrence of the empyema. He was seen 3 months later on a routine follow-up visit and had no evidence of recurrence.

CASE 14. B. K., female, age 58, was admitted to the hospital November 21, 1945; discharged December 22, 1945. Diagnosis: empyema, interlobar, right, streptococcic, postpneumonic.

Two months before admission, the patient was treated for right lower lobe pneumonia with sulfonamides and penicillin. The fever continued and the symptoms returned quite severely 1 week before admission. There was a productive cough with reddish-brown sputum. Examination disclosed rhonchi throughout both lung fields; percussion note normal throughout; a marked arrhythmia with extrasystoles and a question of gallop rhythm. Roentgenograms, November 23, 1945 showed a sharply circumscribed fluid collection with air above it in the right hemithorax posteriorly just above the lung root. The most likely diagnosis was an interlobar, loculated empyema. December 18, 1945, roentgenogram showed marked improvement in the roentgen appearance of the pleural disease with disappearance of the fluid.

The patient was seen in consultation on November 26, 1945, and was placed on systemic penicillin, 100,000 units daily intramuscularly, until December 20, 1945 and penicillin inhalations by aerosol four times daily from November 27, 1945 to December 21, 1945. On November 26, 1945, aspiration of 20 cubic centimeters of pus was done, and 25,000 units of penicillin were instilled into the cavity. This was repeated three times in the next 11 days, 20,000 units of penicillin being instilled each time. Cultures showed a hemolytic and nonhemolytic streptococcus. These organisms were present in all cultures obtained. However, no culture is available for the last two taps. At the time of discharge the patient was markedly improved clinically.

Follow-up: She was seen in the Out-Patient Clinic in August, 1946, at which time she had no complaints, no cough, no hemoptysis, and no chest pain. A roentgenogram taken at this time showed no pathology, except for accentuation of the upper lower lobe septum on the right.

CASE 15. C. S., female, age 27, was admitted to hospital December 3, 1945; discharged May 8, 1946. Diagnosis: (1) bronchiectasis, left lower lobe, lingula, left upper lobe; (2) empyema, postlobectomy, left, putrid, multilocular; (3) fistula, bronchopleural.

This patient had suffered since childhood with a cough which was productive of yellowish, purulent sputum. A foul odor was present at times. In the past year, the symptoms were more pronounced. She also noted profuse, purulent nasal discharge and failure to gain weight. Physical examination revealed an extremely thin and rather tall pallid girl. There was limitation of excursion, dullness and harsh breath sounds in the lower left chest. Bronchograms December 7, 1945, revealed advanced, fusiform and saccular bronchiectasis in the left lower lobe and to a lesser degree in the lingula of the left upper lobe.

Lobectomy of the left lower lobe and the lingula portion of the left upper lobe was performed on December 19, 1945, when a rubber tube drain with

negative pressure was placed in the thoracic cavity. This drain was removed on December 23, 1945. A thoracentesis was done on December 26, 1945 and 240 cubic centimeters of bloody, serosanguineous fluid and some air were removed. Repetition on December 29, 1945 removed 50 cubic centimeters of serosanguineous fluid. On January 1, 1946, 60 cubic centimeters of serosanguineous fluid and 150 cubic centimeters of air were removed. No penicillin was instilled during any of these taps, and the cultures were sterile. However, the postoperative fever continued, with the temperature spiking as high as 103 degrees each day. On January 5, 1946, 60 cubic centimeters of fetid, thick pus were obtained, but no penicillin was instilled, and culture on this material showed Hemophilus influenzae. The tap was repeated on January 6, 1946, and 50 cubic centimeters of viscid, bloody pus were removed with some air, and 50,000 units of penicillin were instilled. On January 7, 1946, the tap was repeated; a few cubic centimeters of bloody fluid were removed and 40,000 units of streptomycin were instilled. On January 8, 1946, 40 cubic centimeters of purulent nonodorous material were removed, and 50,000 units of streptomycin were instilled. On January 9, 1946, 30 cubic centimeters were removed, and 50,000 units of streptomycin were instilled. This was repeated on January 10, 1946, after 50 cubic centimeters of fluid were removed. At this time another cavity was entered anteriorly, and cloudy, purulent-looking material was removed. Culture of this material showed bacteroids, but no other organisms. This cavity was again entered on January 12, 1946, when 35 cubic centimeters of pus were aspirated and 50,000 units of penicillin were instilled. At this time, the fluid from the posterolateral cavity which previously grew the Hemophilus influenzae appeared to be sterile grossly and no streptomycin being available, none was instilled at this time. On January 13, 1946, it was decided that due to the patient's poor clinical response, thoracostomy should be done with insertion of drainage tubes. The patient's course following drainage was poor and protracted, her temperature spiking as high as 104 degrees daily at first and gradually returning to normal following two more attempts at more adequate drainage of this multilocular empyema cavity, many bronchoscopies and much supportive therapy.

Postoperative roentgenograms showed the development of a multiloculated empyema with a large superior-anterior pocket and a posterolateral pocket. These cavities gradually resolved under open drainage. On April 18, 1946, the drainage tubes in the left hemithorax were visible. The left upper lobe appeared to be occupying the remaining space within the left hemithorax. There appeared to be slight increase in the pleural thickening in the axillary region, but no fluid collections were seen to suggest an undrained pocket. The patient received systemic penicillin from December 7, 1945, 150,000 units daily intramuscularly, until January 9, 1946, when the dosage was increased to 350,000 units intramuscularly daily, and continued until February 8, 1946. Sulfadiazine was begun on January 10, 1946 and continued until January 21, 1946, 6 grams daily by mouth. She was finally discharged on May 8, 1946, with obliterated empyema space, no symptoms, and normal temperature.

Follow-up: This patient has been seen in the Out-Patient Department and continues well for 6 months with no evidence of recurrence. Follow-up roentgenograms showed no evidence of recurrence of pleural disease.

Of interest in this patient is the multilocular character of the empyema, the presence of penicillin-resistant organisms in both pockets, and the marked difficulty in adequately draining these pockets, even by direct operative approach.

CASE 16. J. A., male, age 16, was admitted to the hospital, February 2, 1946; discharged February 17, 1946. Diagnosis: (1) empyema, loculated, left; (2) fistula, bronchopleural.

The patient was well until December, 1945, when he developed a cough and pains in the chest accompanied by chills and high fever. His family physician diagnosed pneumonia and treated him at home with sulfonamides with moderate but partial improvement. His weakness persisted, and his high fever returned about the middle of January with much more chest pain. He was admitted to the hospital for further investigation. Examination revealed the chest symmetrical with a suggestion of lag on the left. There was dullness to percussion in the left lung below the fourth rib anteriorly and below the sixth rib posteriorly. Numerous crackling râles were heard in this area, and there were diminished voice and breath sounds. The right lung was clear. Roentgenograms February 4, 1946, revealed abnormal density of the left lower lung field which we believed to be due to a loculated hydropneumothorax. February 14, 1946, improvement had occurred and a thin layer of air was seen between the visceral and parietal pleura in the lateral aspect of the left lower pleural space. There was marked thickening of both layers of pleura. The adjacent parenchymal disease was much less.

Systemic penicillin was begun on February 3, 1946, 200,000 units intramuscularly daily in two-hourly doses, and was continued until February 17, 1946. Thoracenteses, with aspiration of pus and instillation of 100,000 units of penicillin, were done on February 3, 9, 11, 13, and 14. The initial size of the cavity was 100 cubic centimeters. The material removed was thick and nonodorous. There were no positive bacteriologic reports; however, one specimen of pleural fluid, which was sent to pathology, came back with the diagnosis of empyema from the cells and débris which were found. At the last tap on February 14, 1946, only a few cubic centimeters of thin amber-colored fluid were obtained. The sputum volume, which had been 600 to 900 cubic

centimeters per day, decreased to 1 to 10 cubic centimeters per day, and the patient rapidly improved.

Follow-up: This patient was seen 2 months after discharge in the Out-Patient Clinic. He had no complaints. Physical examination revealed marked clearing of the left lower chest, and the roentgenogram was almost normal. The cavity had disappeared and pleural thickening was minimal. Sputum volume remained zero to 10 cubic centimeters per day. We have had no further contact from this patient.

CASE 17. W. D., male, age 46, was admitted to the hospital April 6, 1946; discharged May 13, 1946. Diagnosis: (1) empyema, loculated, left, putrid, postpneumonic; (2) fistula, bronchopleural.

The patient's symptoms began in October, 1945, with malaise, chills, and fever. He was hospitalized and a diagnosis of pneumonia with pleurisy was made. During the 9 weeks of hospitalization, he received numerous thoracenteses with aspirations of fluid. Penicillin systemically was given, but not topically. At the end of 9 weeks, he was sent to another hospital for bronchoscopy and remained there a short time without a diagnosis being made. He returned home for 3 months on no treatment, and during this time he went progressively downhill with productive cough, weight loss, chills, fever, and pain in the chest. Examination revealed a markedly debilitated and emaciated 46 year old white male obviously seriously ill. His color was grayish. He had an old thyroidectomy scar and the trachea was deviated to the right. On the left, expansion was markedly decreased. There was dullness to percussion and the breath and voice sounds were decreased. Roentgenograms April 9, 1946, revealed a large loculated empyema with a fluid level at the left sixth interspace situated posteriorly. There was also what appeared to be a substernal extension of thyroid gland into the superior mediastinum. June 27, 1946, the pleural loculus previously noted had further decreased. There was pleural thickening throughout the left chest. The upper mediastinal mass was still present. There was stringy density in the left lung root.

On admission, this patient was so weak and debilitated he could not move out of bed. His temperature was 101.1 degrees, his pulse 100 and respiration 30. Thoracentesis of this large, loculated pyopneumothorax was done on April 6, 1946, the day of admission, when 1200 cubic centimeters of foul thick pus were removed from the left pleural space and 100,000 units of penicillin were instilled. This treatment was repeated on April 7, 8, 9, 10, and 12, by which time the size of the cavity was 5 cubic centimeters. On April 14, 16, 18, 22, and 27, large amounts of air were removed but no fluid until the taps on May 3, and 7, 1946 when 100 cubic centimeters of fluid and 30 cubic centimeters of air were removed. Penicillin, 100,000 units, was instilled on each of these taps. No other thoracenteses were done. On culture, hemolytic streptococcus, intestinal type, was found on the first specimen, but no anaerobic culture was made. All other specimens were sterile. The patient's temperature dropped rapidly to normal after the first tap, the size of the empyema cavity decreased rapidly, and clinically he improved remarkably. No systemic penicillin was given.

Follow-up: Two weeks after discharge the patient was readmitted to the Orthopedic Service, and roentgenograms taken at this time showed complete obliteration of the cavity and only residual pleural thickening. He was seen again by us on August 10, 1946, at which time his symptoms were minimal and he was able to return to work.

CASE 18. W. A., male, age 56, was admitted to hospital May 26, 1946; discharged July 9, 1946. Diagnosis: (1) carcinoma, pulmonary, left; (2) empyema, loculated, left.

Symptoms of back pain, fever, malaise and pain in the left chest had been present since April 6, 1946. The patient was treated in a local hospital with penicillin and sulfonamides, with some improvement. During this time he had occasional productive cough and some hemoptysis. He was transferred for further study. Examination revealed dullness to percussion and absent breath sounds over the left chest up to the seventh thoracic, with tubular breathing at the apex. The physical examination was otherwise essentially negative. Roentgen-ray examination revealed the following: outside films, the last one on May 4, 1946 showed a roughly spherical mass in the extreme posterior portion of the left lower lobe. Admission film on May 28, 1946 showed evidence of left lower lobe mass which was similar to that seen on the outside film and had increased in size. There was evidence of fluid in the pleural space.

Aspiration removed 70 cubic centimeters of thick, yellowish, nonodorous pus, the culture of which grew a pneumococcus which could not be typed. Penicillin was begun systemically on June 1, 1946 in the dosage of 20,000 units every 2 hours intramuscularly and continued until July 5, 1946. The empyema cavity was tapped and 70 cubic centimeters of pus removed on June 1, 1946. Aspiration was repeated on June 2, 3, 4, and 7. At each tap, 100,000 units of penicillin were instilled. On June 11, 1946, another tap removed 3 to 4 cubic centimeters of noninfected fluid. No penicillin was instilled. The last thoracentesis attempted was on June 18, 1946, at which time no cavity could be found. After the first tap, all other thoracentesis material was sterile. A left pneumonectomy was done on June 20, 1946. No empyema cavity could be found, and the pleura, while thickened, showed no signs of active inflammation. The patient's postoperative course was uneventful, and he was discharged approximately 2½ weeks following the pneumonectomy.

Follow-up: The patient was seen in the office in October, 1946. There had been no postoperative infection in the resected side. He was feeling well, but roentgenogram revealed extension of the carcinoma to the opposite lung. Since then this patient has expired from widespread metastatic carcinoma.

CASE 19. M. H., age 61, was admitted to hospital July 14, 1946; discharged August 16, 1946. Diagnosis: (1) empyema, loculated, left; (2)fistula, bronchopleural; (3) bronchiectasis, upper, middle, and lower lobes, right.

The chief complaint was of cough with blood-streaked sputum. He was well until December 15, 1945, when he developed a cold. This persisted for several days until he became acutely ill and was confined to bed for 5 weeks. Weight loss, sepsis, and productive cough have continued ever since. On physical examination, the temperature was 99 degrees, pulse 115, and respiration 32. The patient was markedly emaciated. There was anterior cervical adenopathy, and the trachea was deviated slightly to the right. The lungs were emphysematous, and there were diminished breath sounds and tactile fremitus over the right base posteriorly. There was some mediastinal shift toward the right. Roentgenograms July 15, 1946, revealed a large loculated fluid collection in left posterolateral chest with fluid level indicative of bronchopleural fistula. August 1, 1946, bronchogram showed extensive saccular bronchiectasis. August 9, no empyema cavity was visible.

Course: This patient was first seen by the Surgical Department on July 14, 1946, at which time thoracentesis was done and 500 cubic centimeters of thick, nonodorous, greenish-yellow pus were removed. Inexhaustible amounts of air were also obtained. Penicillin, 100,000 units, in 25 cubic centimeters of saline was instilled and systemic penicillin, 300,000 units daily, was begun and continued until August 16, 1946. Aspiration was repeated on July 18, 1946 and 500 cubic centimeters of fluid were removed. Evidence of a bronchial fistula was again present. Aspirations were continued on the following days: July 19, 20, 22, 23, and 24, the amount of fluid becoming less and thinner on each of these taps and 100,000 units of penicillin being instilled each time. The taps were continued with instillation of only 50,000 units of penicillin on July 25, 27, 29, 31, and August 2 and 5. At the time of the last tap, only 10 cubic centimeters of air and 2 cubic centimeters of thin, clear fluid were removed from the cavity. Clinical response was rapid and marked during these thoracenteses, and his productive cough cleared rapidly, his appetite returned, and he gained weight. He was strong enough to get out of bed, which he had been unable to do before. None of the specimens of pleural fluid showed any growth. This is interesting since the fluid obtained was grossly pus, and for at least six of the taps there was an open bronchial fistula.

Follow-up: On October 18, 1946, this patient was well, weighed more than he had for a number of years, and had returned to work. His chronic cough persisted but this was probably on the basis of his underlying bronchiectasis. A roentgenogram taken on October 18, 1946, 4 months following treatment, showed no evidence of pleural disease.

CASE 20. I. R., male, age 56, was admitted to hospital October 29, 1946; discharged November 30, 1946. Diagnosis: empyema, loculated, right.

This patient had a previous admission on August 16, 1946 and was discharged on September 6, 1946. Three months before the first admission, the patient noted a knife-like pain in the right chest which was worse upon breathing or coughing. The cough was productive of greenish sputum and he had some night sweats. Examination revealed decreased to absent breath sounds with dullness below the line of the scapula on the right. Roentgenograms August 16, 1946, showed a bilateral pleural effusion, more marked on the right with atelectasis of the right upper lobe out of proportion to the effusion and rounded mass in the right lower lobe area. During this first admission, the patient received intramuscular penicillin, 240,000 units daily, and thoracentesis on August 19, 1946, removed 20 cubic centimeters of putrid, purulent material from the right chest. Penicillin, 200,000 units, was instilled. Bacteriology studies revealed many anaerobic nonhemolytic streptococci. On September 5, 1946, aspiration of a few cubic centimeters of similar material without instilling penicillin was done. The patient was discharged on September 6, 1946 with the cavity still present. At the time of his readmission on October 29, 1946, the patient still had fever and a productive cough. On November 1, 1946, the right chest was again aspirated, and 80 cubic centimeters of greenish-brown fluid with no odor were removed. Bacteriology report on fluid obtained showed a moderate number of Streptococcus viridans. Because of roentgen-ray findings of an additional mass in the right chest, surgical consultation was obtained and exploration of the chest was done on November 18, 1946, revealing only diaphragmatic loculus of empyema which was drained. A biopsy of pleura showed no neoplasm. Streptomycin and penicillin were instilled through the tube daily for 10 days, then the tube was removed. Patient recovered rapidly.

Follow-up: Up to August 25, 1947, approximately 8 months later, the patient was free of symptoms, was gaining weight, and had only slight residual right pleural thickening as shown by roentgenogram.

This patient was treated very inadequately for the 3 months prior to his transfer to surgery. Aspiration was done only twice on his first admission and once on his second hospitalization, although small quantities of putrid pus were obtained each time. On the first and third of these, penicillin, 200,000 units, was instilled. Neither active treatment of the known right empyema or proper proof of the suspected tumor was accomplished. The left effusion was never tapped but disappeared under bedrest, supportive treatment, and systemic penicillin. This case emphasizes the necessity of such patients being treated by the surgeons and is an example of some of the failures reported in other articles.

SUMMARY AND CONCLUSIONS

The thorough aspiration of pus from empyemas and the reinstillation of adequate amounts of an appropriate antibiotic agent satisfy the basic principles of treatment of this disease; namely, sterilization and obliteration of the cavity which can be accomplished in most cases, and re-establishment of pulmonary function thus decreasing morbidity. In the few instances in which the patient does not react satisfactorily, surgical drainage is delayed very little.

In 20 patients treated by us and followed for from 6 to 36 months, cure was obtained in 80 per cent, while 20 per cent required surgical drainage.

Details of a logical and proved technique are described and the contraindications given.

The literature on the subject is briefly analyzed.

The necessity for proper surgical training in order to treat empyema properly by this or other method is emphasized.

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THE EFFECT OF STREPTOMYCIN IN EXPERIMENTAL STRANGULATION OF THE BOWEL

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STRANGULATION of the bowel has been for many years both a diagnostic and a therapeutic problem in surgery. The mortality rate is still high despite the value of intestinal suction, restoration of the fluid and electrolyte balance, and sulfonamides. In experimental bowel obstruction penicillin has proved to be only moderately effective in prolonging life. Streptomycin is of particular value because it is effective against certain pathogenic bacteria which are not susceptible to the action of other antibacterial substances.

The present study was undertaken to determine what effect, if any, was exerted by streptomycin upon the course of experimental strangulation of the bowel in rabbits. We were also interested in ascertaining the extent to which bacteria contribute to the damage of the intestine resulting from an inadequate blood supply.

REVIEW OF THE LITERATURE

It might be helpful at this point to review briefly the literature on the actions of streptomycin as they pertain to the present study. Waksman and his associates (28, 6) have shown that streptomycin is effective against certain gram-negative, gram-positive, and acid fast organisms. Finland and his coworkers have pointed out that many organisms which at first are sensitive to streptomycin may rapidly become resistant. This fact emphasizes the importance of using streptomycin in doses adequate to produce levels in the tissues and body fluids well above the minimum effective concentration.

The parenteral administration of streptomycin can result in a therapeutic blood level which reaches its peak in 1 to 2 hours, and then gradually falls off. Sixty to 80 per cent of the drug is excreted in the urine in 24 hours (21, 30).

There is no absorption from the stomach or bowel. Although streptomycin is less effective in the presence of acids or acid urine, it is not inactivated by gastric juices (1) and, when given orally, is excreted almost entirely in the feces. Large concentrations appear in the feces with a considerable reduction of Bacillus coli and other organisms generally present there (20, 9). Good concentrations of the drug appear in the pleural and peritoneal fluids, bile, aqueous humor, and the fetal circulation (21, 30).

Streptomycin is polyvalent to a much greater degree than penicillin or sulfonamides, and its effectiveness against many strains of organisms of the colon group differentiates it sharply from penicillin (22, 25). Murphy and his colleagues have demonstrated that this property of streptomycin renders it valuable in the treatment of acute diffuse peritonitis caused by a mixture of gram-positive and gram-negative bacteria.

The extent to which intestinal bacteria contribute to the damage to the intestine produced by an inadequate blood supply has not been clearly demonstrated. The recent work of Poth and his group (12, 14, 15, 16, 17, 18, 19) has shown that sulfasuxidine and sulfathalidine have a powerful antiseptic effect on the intestinal flora. Sarnoff and his coworkers (23, 24) concluded that "succinylsulfathiazole conferred a protective effect on a 50 centimeter segment of ileum with occluded venous return, by preventing perforation and permitting recovery of bowel integrity."

Harper and Blain (7) observed that in dogs with isolated, obstructed, jejunal loops death

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Presented in the Forum on Fundamental Surgical Problems before the Clinical Congress of the American College of Surgeons, New York, September 8 to 12, 1947.

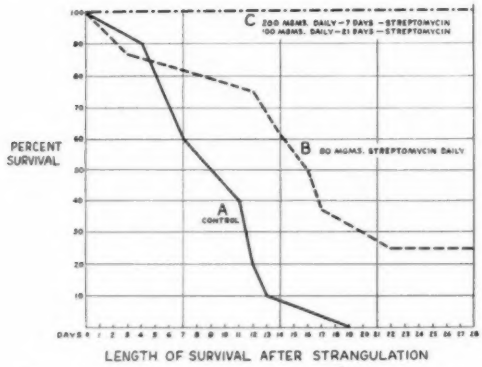

Fig. 1. Effect of streptomycin on mortality rate from bowel strangulation in rabbits.

was due to the action of bacteria or their products, and, furthermore, that these animals could be protected for a significant period of time with large doses of penicillin. Sulfasuxidine, likewise, gives protection in dogs with isolated jejunal loops (13, 8).

Callihan, Kennedy, and Blain (3) emphasized the fact that bacteria play an important part in maintaining the present mortality rate in intestinal obstruction at approximately 20 per cent.

Many investigators (26, 27, 29) have stressed the significance of hemorrhage in shock accompanying strangulated bowel obstructions. In order to study the precise rôle of bacteria, Sarnoff and Fine (23), Blain and Kennedy (2), and others excluded the factor of reduction of the blood volume by treating the shock that developed in their control and experimental animals. While recognizing the significance of hemorrhage and shock, Blain and Kennedy (2) were of the opinion that the bacterial factor was of major importance in causing death from strangulated intestinal obstruction since the survival time was prolonged by penicillin. The prolongation of life, however, though striking, was only moderate. Their control animals died within 36 hours. Seven dogs with the same operation plus massive doses of penicillin survived between 50 and 100 hours. Six dogs lived 70 hours or longer and 4 dogs, 90 hours or longer. In addition, they performed intestinal resections on 5 animals at the end of 72 hours which is twice as long as the survival time for the animals not treated with penicillin, and 4 of these animals lived indefinitely.

MATERIALS AND METHODS

In the present experiments rabbits were used because, as Noer has shown, their mesenteric vascular pattern is more similar to that of man than is the mesenteric vascular pattern of dogs. It was necessary to use a method of producing bowel strangulation which would not introduce the factors of hemorrhage, shock, and intestinal obstruction to complicate the results and render it difficult to determine (1) the exact action of streptomycin upon strangulation unaccompanied by intestinal obstruction, (2) the significance of bacterial growth in producing death from strangulation. For these reasons strangulation by devascularization of the small bowel was the method chosen. The first problem was to ascertain the minimum amount of devascularization of the bowel which would cause death in a high percentage of the animals.

Devascularization was performed by ligating the arcuate artery and vein close to the wall of the ileum at two points of varying distances and then ligating all the intervening blood vessels, so that the only blood to the devascularized area came through the fine intramural vessels at each end. No attempt was made to suture the mesentery because of its thinness. Fifty-two rabbits were operated upon under ether anesthesia, and varying lengths of ileum were devascularized. It was demonstrated (5) that devascularization of 7.5 centimeters of ileum was the smallest length of devascularization associated with a consistently high mortality rate. The average weight of the rabbits in this series was 2 kilograms.

Four groups of rabbits were used. The first was the control series (10 rabbits) in which 7.5 centimeters of bowel was devascularized. The second group (8 rabbits) had 7.5 centimeters of bowel devascularized, and each rabbit was given a single daily subcutaneous injection of 80 milligrams of streptomycin for a period of 25 days. The first injection was given immediately after completion of the devascularization operation.

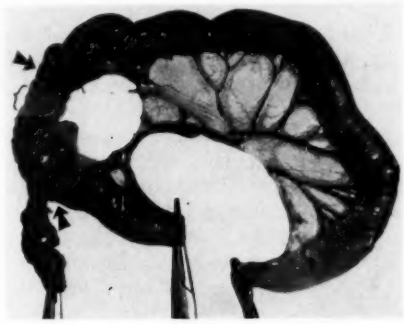

Fig. 2. Gangrene of ileum in untreated rabbit showing site of perforation (bracketed). Note opening in mesentery.

The third group (12 rabbits) had 7.5 centimeters of bowel devascularized, and each rabbit was given 200 milligrams of streptomycin daily for 7 days, followed by 100 milligrams of streptomycin daily for 21 days, given in the form of two subcutaneous injections daily. The first dose was injected immediately after completion of the operation.

The fourth group (5 rabbits) received 100 milligrams of streptomycin daily by subcutaneous injection for 4 days. They were then subjected to devascularization of the bowel (7.5 cm.) and continued to receive 100 milligrams of streptomycin daily for a total period of 25 days.

RESULTS

The effects of varying doses of streptomycin upon the mortality rate in experimental strangulation of bowel in rabbits are presented in Figure 1. The control group of 10 rabbits which had not received streptomycin were dead by the nineteenth day after operation. Postmortem examination disclosed that perforation with peritonitis was the cause of death in 80 per cent of these animals (Fig. 2). In the remaining animals, death did not appear to be directly related to the devascularization of the bowel.

In the second group of 8 rabbits, given 80 milligrams streptomycin daily, the mortality was 62.5 per cent 19 days following operation. There was a definite prolongation of survival time in the rabbits in this group. The deaths could be classified as early and late. The early deaths were due to perforation and peritonitis

Fig. 3. Revascularization of strangulated bowel in streptomycin-treated rabbit. Note thickening and increased vascularity of mesentery, the opening in which has closed.

in 2 animals. The late deaths in 3 animals resulted from intestinal obstruction produced by kinking of the devascularized bowel. In 1 animal, death was not related to the operation. Two animals are still living.

In the third group of 12 rabbits, given 200 milligrams of streptomycin daily for 7 days and then 100 milligrams daily for 21 days more, there has been no mortality after a period of more than 2 months. Five animals were deliberately sacrificed. Postmortem examination disclosed no peritonitis or intestinal obstruction. One animal was alive and apparently well although he had a partial intestinal obstruction.

The changes that take place in the devascularized loops of bowel in those animals which have been enabled to survive by means of streptomycin are of great interest. The 7.5 centimeter loop had contracted to a shorter loop of 5 to 6 centimeters. Blain and Kennedy

Fig. 4. Revascularization of strangulated bowel in streptomycin treated rabbit. Note adherence of vascular omentum to bowel.

(2, 3) have shown the opposite effect, that is, the lengthening of a 60 centimeter segment of ileum to 70 or 100 centimeters when the mesenteric veins were tied. The opening in the mesentery had closed spontaneously. Examination of the devascularized loops of surviving animals showed that the blood supply to the devascularized area came from five sources:

1. Adherent loops of intestine.

2. Growth of mesenteric vessels. The hole in the mesentery had closed and blood vessels had grown up to the devascularized loop of intestine. Figure 3 shows blood vessels which have grown past a ligature.

3. The omentum which was frequently found adherent to the damaged loop (Fig. 4).

4. Vascularized adhesions between the parietal peritoneum and the devascularized loop of bowel.

5. Collateral circulation through the intramural blood vessels. In the fourth group of 5 rabbits given streptomycin before and after devascularization, there was 1 death on the morning after operation, but this was due to a hemorrhagic pneumonia and apparently not related to the experimental procedure. The other 4 rabbits survived. One animal was sacrificed, and postmortem examination showed the same type of revascularization of the devascularized bowel present in group 3.

DISCUSSION

These results indicate that streptomycin is effective in lowering the mortality rate of rabbits suffering from experimental strangulation of the bowel. If a sufficiently large dose (200 mgm. daily) of streptomycin is given, there is no mortality. This action of streptomycin in preventing perforation and peritonitis leads us to conclude that in an area of devascularized bowel (strangulation) gangrene and perforation of the bowel are due more to bacterial invasion of the bowel wall than to lack of blood supply alone. The streptomycin by preventing bacterial invasion of the ischemic area, and thus maintaining the anatomical integrity of the bowel wall, allows time for an adequate collateral blood supply to develop.

It is of interest that in some of the rabbits which received smaller amounts of streptomycin (80 mgm. daily) the pathologic lesion was changed rather than eliminated in the sense that it was changed from a bacterial and ischemic gangrene of the bowel wall to a mechanical obstruction due to kinking of the bowel.

In some respects the bowel lesion produced in these experiments is comparable with acute arterial mesenteric thrombosis or embolism which occurs in human beings. In this condition and in other lesions of the bowel in which there occurs a combination of inadequate blood supply and bacterial invasion of the tissues—for example, after operative release of a strangulated hernia or after intestinal suture or anastomosis when the vascularity of the tissues at the site of suture is in doubt—the administration of streptomycin may, on the basis of the results of the present study, prove to be of value.

Finally, the question must be asked: How does the streptomycin reach the bacteria present in the devascularized area? There are two possible ways in which this could take place: (1) The streptomycin is secreted into the intestinal tract in effective concentration from the blood stream. It has been shown that streptomycin administered parenterally is not excreted into the intestine. In our experiments streptomycin was not administered orally. (2) The streptomycin is carried in the blood stream along the collateral blood vessels which run from the normal bowel into the devascularized area. This is the probable route. We have shown elsewhere (5) by injection studies that the intramural vessels remain patent and carry blood into the devascularized area of bowel.

If this explanation is correct, namely, that—the action of streptomycin in bowel strangulation depends upon its being carried to the strangulated area by the blood stream, it follows that the more extensive the area of strangulation the less likely is streptomycin to prove effective in preventing bacterial gangrene and perforation of the bowel wall. In a paper which will be published elsewhere (5), we have shown that the length of survival is directly inverse to the length of strangulated bowel. This would mean that the more extensive the strangulated loop, the shorter would be the period of survival, and, therefore, less

time would be available for the streptomycin to exert a beneficial effect.

These facts have a direct clinical application. Since it is usually impossible to predict before operation the extent of strangulation which is present, it would be dangerous to depend upon streptomycin alone even in patients with mesenteric thrombosis. It is clear that streptomycin should be regarded as an adjunct to rather than as a substitute for surgery in strangulation of the bowel.

CONCLUSIONS

The administration of streptomycin in doses of 80 milligrams (40 mgm. per kilogram of body weight) daily lowered the mortality rate, and in doses of 200 milligrams (100 mgm. per kilogram of body weight) daily prevented any mortality in rabbits subjected to experimental strangulation of bowel by devascularization.

Bacterial growth in the devascularized bowel wall was the major factor leading to perforation and gangrene of the bowel. Prevention of the growth of bacteria by streptomycin was the mechanism underlying the prolongation of life in the treated rabbits in these experiments.

On the basis of the results obtained in our study, it is suggested that in human beings the administration of streptomycin might be a useful adjunct in the treatment of strangulated intestinal obstruction, particularly the type due to acute arterial mesenteric thrombosis or embolism. Streptomycin should be given in intestinal obstruction when strangulation is suspected. It is suggested that the therapeutic value of streptomycin is dependent upon the length of strangulated bowel. Since it is impossible to predict the extent of strangulation, streptomycin should be regarded as an adjunct to and not as a substitute for surgery.

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THE "BURIED EPIDERMIS" GRAFT

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THE purpose of this paper is to revive an old, yet simple and efficient, method of skin grafting and to discuss its application to the problem of the treatment of bedsores in patients suffering from paraplegia. The procedure has been used for more than 2 years (E. B.) in selected decubitus ulcers. The last series of more than 50 patients treated during the past year forms the basis for our observations.

The procedure is known as the "Implantation Method of Skin Grafting" (Wangensteen). Originated by Braun (5,6) in 1920, it was applied by Wangensteen for the first time in 1928. In 1930 he reported the technique, indications, and results in 60 cases. The series included cases of infection, osteomyelitis, empyema cavities, decubitus ulcers, and burns. As we have been familiar with the method since 1929, it seemed that we were justified in using it on a larger scale in treating decubitus ulcers in the presence of spinal cord injuries.

The sores treated were situated on the sacrum, trochanters, knees, ankles, ischium, dorsum, and iliac spine. The purpose of the grafting was twofold: first, to achieve permanent closure of the ulcer, and, second, to provide temporary epithelization in order to restrict the loss of proteins until a permanent plastic flap procedure could be attempted. The use of buried epidermis as a permanent graft has definite value in cases in which plastic procedures cannot be executed. The method is well suited for the treatment of ulcers of the heels, ankles, and knee caps.

The preoperative management is similar to, though less complicated than, the routine preparation for plastic closure of decubitus ulcers. It consists of maintaining the protein balance (14) and correction of anemia (11). Also wet dressings of Dakin's or Domboro's solution are applied locally, to the area involved to enhance good granulation; better granulation tissue provides a better medium for the seeds to develop in. Wangensteen's observation, however, confirms the fact that there is a surprising number of "takes" even when the seeds are implanted in a poor host.

The technique (Fig. 1) is essentially the same as that described by Braun and Wangensteen. After routine preparation of the donor site with ether and alcohol, saline solution is used to keep the skin surface wet. With a Ferris Smith or amputation knife a thin Thiersch graft is removed in one piece; its size depends on the number of grafts needed. The graft is then divided on a wooden board with a Parker knife into small squares of 0.3 by 0.3 centimeter. An instrument is used to drill holes into the granulation tissue, at an angle of 35 degrees. The grafts are introduced into the preformed bed where they are retained after withdrawal of the instrument. Instead of the instrument, straight needles can be used, as described by Wangensteen. It is best to implant the seeds first into the lowermost row of the field. This step will keep the operative area free of blood. Even the slightest, unavoidable hemorrhage from burrholes tends to blur the field if grafting is started on top. The grafts are placed 1 to 1.5 centimeters apart. The grafted area is covered with dry fibrin foam and then dressed with equal parts of furacin and boric acid ointment. A firm bandage is applied for 5 to 7 days. The dressings are changed every other day. Should pyocyaneus infection develop despite the prophylactic use of boric acid ointment, acetic acid wet dressings will readily eliminate it. We keep the patient in bed for 48 hours although Wangensteen has applied the method successfully in ambulatory patients. At the end of the first and beginning of the second week, grayish islands (Fig. 2) of epithelium appear at the site of the seeds. The patches coalesce rapidly and the granulation tissue retracts. If barren spaces are left, regrafting can be at-

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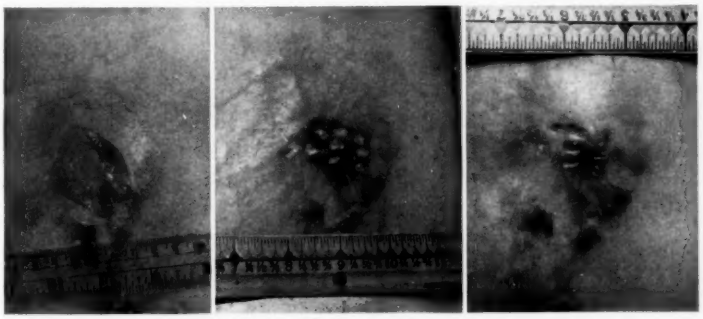
a b c

Fig. 1. a, Method of obtaining Thiersch graft from surface of thigh; b, method of dividing Thiersch graft into seeds; c, method of implanting seeds.



a b c

Fig. 2. a, Before grafting; b, 15 days after grafting; c, 28 days after grafting.

tempted at any stage after the first 10 days. Complete epithelization will take place in from 3 to 6 weeks depending on the size of the defect.

We concur with Wangensteen's statement that the "cosmetic result has not been above criticism," and we also agree with him that this disadvantage is outweighed by the many advantages. The chief advantages are (1) the simplicity of the method; (2) the great number of "takes" ranging from 50 to 70 per cent; (3) the resistance of the implants to infection and extrinsic damage—even where breakdown occurs, quick regeneration ensues from the seeds; (4) the thriftiness of the method—the donor area, in other words the size of the Thiersch graft, need be only 6 to 8 per cent of the size of the defect to yield sufficient seeds to bring about healing.

Comparison of the resulting skin with that obtained by marginal epithelization showed it to be firmer and stronger. Under gentle massage the skin revealed a tendency to become mobile. The reason for that might be an imitation of true skin by the seeds (4) which tend to push their epithelium along the cleft created by the implantation. On histologic examination berrylike structures were described (15) consisting of a nucleus of cutis enveloped by a shell of epidermis. This too undoubtedly accounts for easy regeneration.

All these advantages more than outweigh the criticism that the cosmetic results are inferior and that the quality of the resulting skin is inferior to that obtained with plastic flap procedures. It is our opinion, therefore, that in all cases of decubitus ulcer where free skin grafting appears to be indicated, the "buried

epidermis" graft is far superior to any other type of free skin graft.

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THE TREATMENT OF CONGENITAL (OR DEVELOPMENTAL) COXA VARA

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ONE must conclude from a critical review of the literature that the treatment of congenital coxa vara is not too well defined. There are those who recommend a period of conservative treatment prior to surgery. It appears logical to these authors (2, 10) that protection from direct weight bearing in unilateral cases and the avoidance of the upright position in bilateral cases may lessen the deforming effects which weight bearing and muscle tension have upon the disorganized femoral necks in these cases. Although they report no group of patients so treated, they draw attention to the fact that spontaneous correction has been observed to occur in other types of juvenile coxa vara, for example, the rachitic type, and also to the fact that a mild varus deformity of the neck of the femur is consistent with good function (Fig. 1).

However, most authors believe that there is no justification for awaiting spontaneous ossification prior to osteotomy and they advise immediate surgical intervention (3). In this latter group there are those who favor (12) and those who advise against (4, 5, 9) drilling or introduction of a bone peg through the femoral neck and epiphysial plate region for purposes of "revascularization" and "revivification," prior to or at the time of corrective osteotomy Those recommending osteotomy alone point to the fact that overcorrection of the neck deformity to a degree of coxa valga, so as to bring the plane of the capital epiphysial line nearer to the horizontal, has been followed by spontaneous maturation of the epiphysial plate in their patients.

The present investigation is based upon 17 cases of the congenital or developmental type of coxa vara, and it has as its purpose an evaluation of the results following a variety of surgical procedures. The ages of the 17 patients ranged from 3½ to 21 years at the time of first operation. In 8 patients the condition was bilateral and in 9 it was unilateral.

From the Laboratory Division, Hospital for Joint Diseases, New York, Henry L. Jaffe, M. D., director. Work done under a Frederick Brown Research Fellowship in Orthopedic Surgery.

ANALYSIS OF CLINICAL MATERIAL

The clinical data in the 17 cases of congenital (developmental) coxa vara have been incorporated in Table I. Results were interpreted as being good when pain was relieved, limp and a positive Trendelenburg test lessened or disappeared, the normal lumbar lordosis was restored, the range of abduction of the hip joint was increased, and there was restoration of some or all of the length of the affected extremity. The roentgenograms in these cases revealed a restoration of the normal neck-shaft angle of the femur. Such results were obtained in 2 cases, one being unilateral and the other being bilateral. Fairly satisfactory results, as judged from the facts that some residual deformity and disability persisted postoperatively, often with incomplete correction of the coxa vara deformity on the roentgenogram, were obtained in 4 cases, 2 being unilateral and 2 being bilateral. The results in the remaining cases have been classified as poor.

DISCUSSION

The postoperative results in the 17 cases of congenital coxa vara herein reported have not been uniformly satisfactory after any one method. However, they have been more consistently satisfactory, with a lesser incidence of immediate postoperative complications, following subtrochanteric osteotomy than by any other procedure. The poorest results have followed the intra-articular procedures.

The appearance of late complications, such as deformity of the femoral head and degenerative arthritis of the hip joint, was related

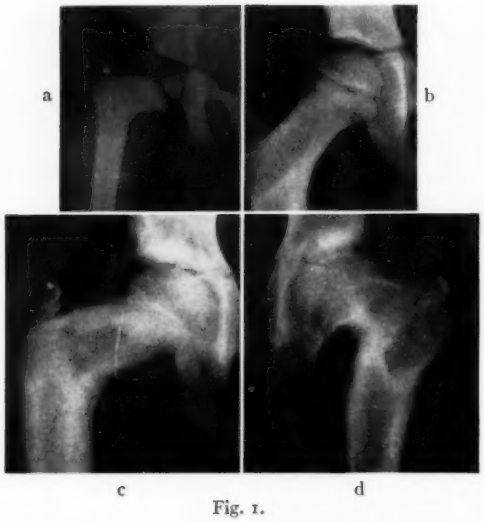

Fig. 1.

Fig. 2.

Fig. 1. a, Anteroposterior roentgenogram of the right hip joint in a 21 month old colored boy with bilateral coxa vara deformity on a rachitic basis. b, Roentgenogram of the same hip 6 years later, during which period the child received no orthopedic treatment, shows an overcorrection of the femoral neck deformity with the development of slight coxa valga. A similar spontaneous correction occurred on the left side. c, Roentgenogram of the right hip joint in an 11 year old male demonstrating open epiphyses and a moderate coxa vara deformity. There has been no surgical intervention on this side and the function is excellent. d, Roentgenogram of the left hip joint in the same case as (c), 2 years after a drilling operation and subtrochanteric osteotomy. The capital and greater trochanteric epiphyses are closed and the coxa vara deformity is fairly well corrected. Function is excellent and there is only a slight limp on this side.

Fig. 3.

Fig. 2. a, Right hip joint of a 7 year old colored female. There is a marked congenital coxa vara deformity, and the region of the vertically placed epiphysial plate and of the adjacent femoral neck shows considerable disorganization. The projecting inferior lip of the femoral neck could be misinterpreted as representing the inferior portion of a displaced capital femoral epiphysis. b, Same hip joint as in, a, 2 years following subtrochanteric osteotomy. The functional result is poor, there being residual limp and considerable loss of motion. The roentgenogram shows a residual coxa vara, and mushrooming of the capital epiphysis with narrowing and irregularity of the joint space superiorly. c, Hip joint in a 31 year old girl with severe bilateral coxa vara deformity, 9 years after a subtrochanteric osteotomy. The femoral head is somewhat mushroomed and the joint space is narrowed superiorly. d, Roentgenogram of the right hip joint in the same patient as (c), 15 years after a Whitman reconstruction operation for a marked congenital coxa vara deformity, demonstrates a very advanced degenerative arthritis of the hip joint.

Fig. 3. a, Roentgenogram of the left hip joint of a 7 year old boy, 1 year after replacement of the capital epiphysis on the femoral neck with a bone peg. The capital fragment has collapsed and there is severe distortion of the remains of the femoral head and neck. Clinically, the hip joint was ankylosed with a flexion-adduction deformity which required a subtrochanteric osteotomy. b, Right hip joint in a 7 year old colored female in whom the bony structures are remarkably well developed. The coxa vara deformity is severe, the inferior border of the femoral head reaching below the level of the lesser trochanter. The femoral neck is somewhat foreshortened, and its inferior beak projects sharply downward as far as the inferior tip of the capital epiphysis.

(*Continued on next page*)

not only to the severity and duration of the coxa vara deformity and to the age of the patient, but, in some of the cases, to the surgical intervention. These complications occurred not only following intra-articular procedures (Figs. 2 b and 3 a) but followed a combined drilling-subtrochanteric osteotomy with revision of the greater trochanter in one case (Fig. 3, e and f) and subtrochanteric osteotomy in 3 cases (Figs. 2 a, b, d and 3 b, c, and d). It is apparent from the writer's material, therefore, that a good clinical result immediately postoperatively is no assurance against the development of secondary degenerative changes in the hip joint later in life. Nevertheless, these changes will certainly appear and at a much earlier age (as early as 15 years in one case in the writer's material) if no effort is made to correct the mechanical disturbance incidental to the coxa vara deformity.

Discussions relative to the technical problems involved in performing a subtrochanteric osteotomy and underlying the rationale of drilling as a procedure directed to revascularizing and revivifying osseous tissue, and with reference to the treatment of cases in which a severe degenerative arthritis of the hip joint dominates the clinical picture, require special consideration.

TABLE I.—CLINICAL DATA IN 17 CASES OF CONGENITAL COXA VARA

Operation	Age	Unilateral or bilateral	Result	Remarks
Subtrochanteric osteotomy	3½	Bilateral (rt.*)	Good	Follow-up 4 years. Drilling osteotomy on left
	11	Bilateral	Fair	Follow-up 4 years
	6½	Unilateral	Fair	Follow-up 3 years
	7	Unilateral	Poor	Required second osteotomy with fair result
	6	Bilateral	Poor	Pseudarthrosis followed second osteotomy
	7	Bilateral	Poor	Required second osteotomy
	7	Bilateral (rt.*)	Poor	Partial ankylosis of right hip joint. Drilling osteotomy on left
	21	Bilateral (left*)	Fair	Observed 9 years postoperatively. Beginning degenerative joint changes. Whitman operation on right
Drilling of femoral neck and subtrochanteric osteotomy	5	Unilateral	Good	Two stage operation. Follow-up 2 years
	3½	Bilateral (left*)	Good	One stage operation. Follow-up 4 years
	9	Bilateral	Fair	One stage operation, with removal great trochanter. Follow-up 2 years
	5½	Unilateral	Poor	Required second osteotomy with good correction, one stage
	7	Bilateral (left*)	Poor	Partial ankylosis of hip joint. One stage
	5	Unilateral	Poor	Two stage operation. Loss of control of fragments and abduction contracture of hip joint
	14	Unilateral	Poor	Follow-up 8 years. Painful hip due to degenerative arthritis
Bone graft and subtrochanteric osteotomy	10	Unilateral	Poor	Required second osteotomy. No follow-up
Bone peg with reposition of femoral head	7	Bilateral	Poor	Left side only. Postoperative infection resulted in ankylosis of both hip joints
Bone peg through head and downward shift of great trochanter.	7	Unilateral	Poor	Ankylosis of hip joint with flexion-adduction deformity
Whitman operation	15	Bilateral (rt.*)	Poor	Follow-up 15 years. Pain and disability
Resection of portion of epiphysial plate	6	Unilateral	Unknown	Epiphysiodiaphyseal fusion obtained. Did not return for subsequent osteotomy

* Bilateral cases with different operations on each side.

Subtrochanteric osteotomy. On theoretical grounds, a postoperative recurrence of coxa vara deformity might be anticipated in a young patient whose roentgenograms demon-

The vertical epiphysial plate and the metaphysis appear fairly well organized. c, Excellent correction of the coxa vara in the case illustrated in, b, after subtrochanteric osteotomy. The epiphysial plate is still visible. d, Roentgenogram of the hip joint in, c, 1½ years postoperatively, demonstrates marked alteration in the head and neck of the femur. The bone is markedly densified, the neck is broadened due to the deposition of bone on its superior surface, and the head is deformed and its articular surface is irregular. e, An advanced stage of coxa vara deformity in a 14 year old male with unilateral involvement. The neck is markedly foreshortened and the inferior portion of the femoral head is placed opposite the lesser trochanter where it appears to be attached directly to the femoral shaft. There is an irregular, radiolucent band between the femoral head and the remains of the disorganized neck, which might be misinterpreted as a site of pseudarthrosis or nonunion. f, Roentgenogram of the hip joint in the case illustrated in, e, 5 years following a drilling of the neck of the femur, subtrochanteric osteotomy, and excision of part of the greater trochanter. The immediate correction of the coxa vara was very good, and, in fact, this roentgenogram demonstrates the outlines of the head and neck in the corrected position. There has occurred, however, an enormous deposition of bone about the femoral neck, particularly at the upper pole of the resected greater trochanter. The femoral head is mushroomed and its articular surface is irregular.

strate a highly disorganized epiphysial plate and femoral neck at the time of osteotomy, because of progressive activity of this underlying lesion. Recurrence of varus deformity was observed in this study in 4 patients, whose ages ranged from 5½ to 7 years. However, this complication was observed immediately or shortly after operation in all instances and was due to inadequate or improper control of the postosteotomy fragments. Indeed, the fact that progression of varus deformity did not occur in the femoral neck, once union occurred following subtrochanteric osteotomy, and that the epiphysial plate regions appeared to mature spontaneously in these cases, lends support to those who advocate subtrochanteric osteotomy alone without supplemental drilling of the femoral neck in the treatment of congenital coxa vara.

Recurrence of the varus deformity immediately following subtrochanteric osteotomy is due to certain mechanical difficulties encountered in the control of the postosteotomy fragments. When a subtrochanteric or intertrochanteric osteotomy is performed in the presence of an ankylosed hip joint, the position of the femoral fragments is easily controlled by adequate external fixation (plaster of paris) because the short proximal fragment is fixed. When such an osteotomy is done in the presence of a movable hip joint, it may be difficult to control the proximal fragment, the head and neck rotating as the distal fragment is abducted (8). This difficulty prevails whether the osteotomy is transverse or oblique, with or without excision of a lateral wedge of bone, or is curvilinear, V-, L- or Z-shaped, procedures designed to prevent displacement of the osteotomy fragments. Furthermore, in order to correct a varus deformity of 90 degrees or less, the thigh would have to be abducted to a position in relation to the fixed pelvis which is impossible except in very young infants because of the restricting ligaments and adductor muscles, unless so much bone is sacrificed as to jeopardize control of the femoral fragments and to encourage increased shortening (9).

To obviate these difficulties, the long axis of the proximal femoral fragment should be maintained in its proper relation to the pelvis, leaving the abnormal relation of the femoral shaft to the neck to be corrected by bringing the major distal fragment into the necessary degree of abduction. Control of the proximal femoral fragment may be secured by the use of a stainless steel pin incorporated in the plaster of paris encasement or stainless steel pins or Schanz screws in both fragments may be fixed to each other by a Riedel plate or some modification thereof and incorporated in the plaster encasement (9). On the other hand the femoral fragments may be fixed to each other internally by the use of a Blount or Moore type of metal plate (1). A well-leg traction apparatus may be used after osteotomy to control the distal fragment by traction in cases in which the hip joint is mobile and particularly where the contractured soft tissues and muscle spasm prevent immediate correction of the deformity (8, 11).

Drilling of, or implantation of a bone peg through, the femoral neck. The rationale of drilling the femoral neck or introducing a bone graft through it into the head as measures to revascularize and revivify bone, as recommended, for example, in the treatment of degenerative arthritis of the hip joint, has not been sustained by clinical experience (6) or by the writer's histologic studies. Histologic sections from the femoral head in several cases of degenerative arthritis of the hip joint and of Perthes' disease treated by multiple drillings, indicate that these drill holes persist for years, become filled with connective tissue, and in no way modify the progress of these disease processes. Nor is it clear how a piece of transplanted bone, avascular in itself, will aid in the process of revascularization.

Treatment of secondary severe degenerative arthritis of the hip joint. Cases with severe coxa vara of long duration pose the additional problem that a good surgical correction of this deformity may fail to effect a satisfactory functional result in the presence of secondary degenerative changes in the femoral head and hip joint. The use of arthrodesis in unilateral cases and of vitallium cup arthroplasty or resection of the femoral head in bilateral cases as discussed by the writer for the treatment of degenerative arthritis of the hip joint (7), would appear to apply also to the late cases.

CONCLUSIONS

1. This investigation is based on 17 cases of congenital or developmental coxa vara. This deformity should be suspected in any child who manifests a painless limp. Pain which appears in adolescence and in the adult is dependent on the degree of deformity and shortening, and upon the extent of degenerative changes which affect the hip joint largely on a static basis. The roentgenograms and histologic studies in these cases show a pronounced disorganization of the femoral neck in the region of, and distal to, the epiphysial plate, the exact nature of which is not clearly understood.

2. An evaluation of the results of surgery in these 17 cases of congenital or developmental coxa vara fails to justify the use of drilling of, or introduction of a bone graft through, the femoral neck as a procedure supplemental to corrective osteotomy. The results have been satisfactory more consistently, with a lesser incidence of immediate postoperative complications, following simple subtrochanteric osteotomy than by any other method. Recurrence of coxa vara deformity after subtrochanteric or intertrochanteric osteotomy in 4 cases was due to mechanical difficulties involving control of the postosteotomy fragments, particularly in the presence of a movable hip joint. A good surgical correction may be vitiated in cases in which the coxa vara deformity has been of long duration and the follow-up period sufficiently long, as a result of the appearance of secondary degenerative changes in the femoral head and hip joint.

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THE EFFECT OF TETRA-ETHYL AMMONIUM CHLORIDE ON GASTRIC SECRETION AND ACIDITY IN PEPTIC ULCER

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THE excessive secretion of acid gastric juice at night when the stomach is empty of food has been shown by Dragstedt to be a major contributing factor in the origin and particularly in the continuing activity of peptic ulcers. He has further shown that the amount of free stomach acid and the volume of the night gastric secretion are excessive in patients with peptic ulcer as compared with normal persons or patients with other diseases. To decrease this night secretion, Dragstedt (4, 5, 6) devised an efficient method of sectioning the vagus nerves to the stomach. This operation has proved to be effective in its purpose. Following complete section of both vagus nerves, a marked decrease in the secretion of acid gastric juice has been uniformly observed. Unfortunately, however, the effects of vagus section have not been entirely beneficial. Grimson (9), Moore (8), Walters (10) and other experienced observers have reported postoperative gastric atony, dysphagia, bouts of diarrhea, and certain other unpleasant gastrointestinal manifestations.

Because of these unfortunate effects of vagus section, it occurred to the author that a method of temporary vagal block might effectively decrease the excessive night gastric secretion in the patient with peptic ulcer without interfering with vagal function during the day when acid gastric juice and peristaltic activity are needed in the processes of digestion.

The published investigations of Acheson, Moe, Lyons, and their co-workers (1, 2, 3, 7) indicate that tetra-ethyl ammonium salts produce an effective block of all autonomic nerve impulses, both sympathetic and parasympathetic, and that this block occurs at the autonomic ganglia. One of the many effects of this block is reported to be a decrease in gastrointestinal motility and in the volume and acidity of the gastric juice.

With these preliminary thoughts, an investigation was undertaken to determine whether the excessive night secretion in patients with peptic ulcer could be prevented by vagus nerve block with tetra-ethyl ammonium chloride (etamon). In evaluating the results of this investigation it must be kept in mind that the block produced by etamon is not a pure vagal block but a combination of vagal plus sympathetic block.

Sixteen patients with peptic ulcers proved by x-ray examination or gastroscopy were selected at random from the hospital wards. Eleven of these patients had duodenal ulcers, 3 had marginal ulcers at the sites of previous gastroenterostomies, 1 had a gastric ulcer, and 1 had multiple gastric ulcers. One of the patients with duodenal ulcer was tested twice (No. 10 in Table I), and he subsequently proved at operation to have a giant follicular lymphosarcoma of the stomach in addition to a duodenal ulcer. In the cases of marginal ulcer the measurement of the 12 hour secretion is less reliable because of the presence in each of these cases of a gastroenterostomy.

The following schedule was carried out on each patient:

The usual hospital supper was given at 5:00 p.m. Nothing by mouth was allowed thereafter until the completion of the gastric drainage on the following morning. At 8:30 p.m. a gastric lavage was done through a large caliber tube until the return was clear. Continuous nasogastric suction was then carried out from 9:00 p.m. to 9:00 a.m. The total 12 hour volume of the suction drainage was measured and determinations of the free and total acidity were made.

On the succeeding night the same procedure was repeated with the added factor of intra-

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Presented in the Forum on Fundamental Surgical Problems before the Clinical Congress of the American College of Surgeons, September 8-12, 1947.

TABLE I.—TWELVE HOUR NIGHT GASTRIC SECRETION AND ACIDITY

Patient	Intramuscular etamon dosage		Without etamon			With etamon		
	Mgm. of etamon per kgm. of body weight	Interval of administration	Volume in c.c.	Units of free acid	Units of total acid	Volume in c.c.	Units of free acid	Units of total acid
1. K.H.	20.5	One dose	630	75 (Five hour secretion)	103	200	20 (Five hour secretion)	50
2. L.P.	18.9	Every 6 hours	1210	78	103	270	24	46
3. E.L.	19.9	Every 6 hours	1026	9	38	2000	52	80
4. D.R.	20	Every 6 hours	568	6	32	110	0	13
5. J.M.	20.1	Every 6 hours	750	29	48	450	0	29
6. C.T.	20.6	Every 6 hours	475	0	33	19	0	11
7. C.L.	21	Every 6 hours	520	0	22	360	19	43
8. N.A.	21	Every 6 hours	1500	75	107	460	48	79
9. L.H.	21.6	Every 6 hours	1000	35	60	650	47	106
10. E.T.	17.9	Every 6 hours	545	30	86	550	0	34
	17.9	Every 4 hours	600	24	40	160	15	37
11. H.J.	18	Every 4 hours	875	59	90	400	0	36
12. A.M.	18.9	Every 4 hours	1000	15	40	680	10	23
13. M.G.	19.1	Every 4 hours	1450	30	53	115	21	44
14. K.B.	19.1	Every 4 hours	550	31	53	490	39	61
15. A.L.	19.5	Every 4 hours	740	10	28	345	8	27
16. A.S.	20.5	Every 4 hours	925	26	45	425	13	35

muscular etamon. The doses of etamon varied from 17.9 to 21.6 milligrams per kilogram of patient's body weight. The doses were given at 6 hour intervals (at 9:00 p.m. and 3:00 a.m.) in 8 patients, and at 4 hour intervals (at 9:00 p.m., 1:00 a.m., and 5:00 a.m.) in 6 patients. One patient was tested twice, once at 6 hour intervals and once at 4 hour intervals. The first patient was tested for 1 night only, drainage being obtained for 5 hours without etamon and for 5 additional hours following a single dose of etamon.

The etamon dosage employed and the results of the investigation are shown in Table I.

Very few side effects of etamon were noted—all were transient and none was serious. Among these side effects were blurring of vision in 2 patients, a "shaky" or "jumpy" feeling in 1 patient, and a temperature of 101.6 degrees with moderate cellulitis of both buttocks at the injection sites in 1 patient. Blood pressure readings were checked in about half the cases and there was always a drop about 1 hour after each dose of etamon. This drop varied from 7 to 34 points in the systolic pressure and from 2 to 22 points in the diastolic pressure. This drop was transient and the pressure returned to normal within 3 to 4 hours.

SUMMARY

Effective reduction of the 12 hour night secretion or acidity or both was accomplished in 12 out of 17 gastric drainage tests done with the administration of intramuscular etamon. Two tests failed to effect a significant reduction in either secretion or acidity, 2 other tests resulted in a significant decrease in the volume of secretion but a rise in the levels of both free and total acid, while another test showed no change in secretion but a definite decrease in the free and total acidity.

Nine tests were done with etamon given at 6 hour intervals. Of these, 1 did not show a significant decrease in secretion or acidity, 2 showed a decrease in secretion but an increase in acidity, and 1 resulted in decreased acidity but an unchanged volume of secretion.

Seven tests were done with etamon dosage at 4 hour intervals, and only 1 failed to show a decrease in secretion or acidity. The diagnosis of marginal ulcer in this last patient was not clear-cut.

In 1 case a marked decrease was exhibited in both secretion and acidity for the 5 hours following a single dose of etamon.

The slight variation in the milligram dosage was dictated by the necessity of measuring the dose in cubic centimeters for injection. No difference in results could be attributed to this slight variation which was present in the milligram dosage.

In determining the adequacy of the dosage interval it is of interest that Case 10 was tested twice, once at 4 hour intervals and once at 6 hour intervals. This patient showed a poor response to etamon dosage at 6 hour intervals but a very good response when the dose was repeated at 4 hour intervals.

CONCLUSIONS

1. Tetra-ethyl ammonium chloride (etamon) prevented excessive night gastric secretion and acidity in 12 out of 17 tests of patients with peptic ulcer studied.

2. Intramuscular etamon dosage of approximately 20 milligrams per kilogram of body weight is usually adequate to produce the above effect if repeated at intervals of 4 hours but is not uniformly adequate at intervals of 6 hours.

3. When etamon was given at 4 hour intervals, excessive night gastric secretion and acidity were inhibited in 6 out of 7 patients with peptic ulcer.

4. No serious toxic or side effects of etamon were noted.

5. Transient fall in both systolic and diastolic blood pressures was noted after etamon administration.

6. Therapeutic trial of the effect of etamon on the symptoms and healing of peptic ulcers is warranted and will be undertaken.

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TRANSITION OF PANCREATIC EDEMA INTO PANCREATIC NECROSIS

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THE usual pathogenetic mechanism of acute pancreatitis in man is a block at the papilla of Vater in the presence of a common channel between common bile duct and pancreatic duct. This block, caused either by stone or by spasm, will lead to stagnation of pancreatic juice and of bile in the common channel. The subsequent increase of pressure in the duct system and the intraductal activation of pancreatic juice are considered to be the causes of acute pancreatitis.

The authors have demonstrated the presence of a common channel in 89 per cent of a series of cases of pancreatic edema, of acute pancreatitis and of pancreatic necrosis (3). This finding together with the observation that transition of pancreatic edema into acute pancreatitis occurred not so rarely made us feel that basically, these processes were not different. Why, however, in some cases edema of the pancreas would develop and in others hemorrhagic necrosis, remained to be answered.

After we had succeeded in producing experimentally an extensive edema of the pancreas under conditions resembling physiologic processes (4), the question arose how this same mechanism would lead to the development of pancreatic necrosis. Our method of producing pancreatic edema consisted in stimulation of external pancreatic secretion by intravenous injection of a large dose of secretin after ligation of the main pancreatic duct or of the main and accessory ducts. Though this procedure rarely failed to produce edema of the pancreas, it never caused pancreatic necrosis.

Similar experiments with stronger and more prolonged stimulation of pancreatic secretion by constant intravenous infusion of secretin solution over several hours, or by repeated administration of large doses of secretin at short intervals over a period of several hours, did not lead to pancreatic necrosis.

We had felt heretofore, that pancreatic edema and acute pancreatitis were probably different reactions to, or different degrees of, the same process. However, the observation that secretin produced edema only and never produced pancreatitis, suggested that an additional factor was necessary to transform pancreatic edema into pancreatitis or pancreatic necrosis.

The following procedures designed to transform pancreatic edema into pancreatic necrosis, gave negative results: Ligation of the cysterna chyli in order to block lymphatic drainage from the pancreas; temporary clamping of the portal vein; shock produced by trypsin or by gross trauma. However, temporary occlusion of the main pancreatic (gastroduodenal) artery, performed in animals with edema of the pancreas, led to the development of pancreatitis. In order to make sure that this occlusion of the pancreatic artery by itself would not cause necrosis of the pancreas, preliminary control experiments were performed which showed that this procedure, applied for 30 to 45 minutes in a normal dog, was not followed by gross or microscopic changes of the pancreas.

METHODS

Seventeen healthy mongrel dogs of both sexes, weighing between 9 and 13 kilograms, were used. The animals were anesthetized with pentobarbital sodium and aseptic technique was used throughout operation. In 10 dogs edema of the pancreas developed following secretin injection and the main pancreatic artery was occluded for 15 minutes. The remaining 7 dogs served as controls: (a) without pancreatic edema arterial occlusion was performed after ligation of the pancreatic duct or after injection of secretin; (b) with pancre-

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Aided by a grant from the A. B. Kuppenheimer Fund. The Department is in part supported by the Michael Reese Research Foundation.

TABLE I.—CONTROL SERIES

Dog No.	Duct ligation	Secretin injection i. v.	Arterial occlusion (15 minutes)	Edema*	Postoperative day sacrificed	Gross findings	Histologic findings
1	+	+	o	++	5	o	o
2	+	+	o	+++	6	o	o
3	+	+	o	++	3	Pancreas somewhat indurated	o
4	+	o	+	o	6	o	Beginning cirrhosis of pancreas
5	+	o	+	o	3	Pancreas indurated	o
6	o	+	+	o	5	o	o
7	+	+	+	o	8	o	o

*Edema: +moderate; ++marked; +++very marked.

atic edema, but without occlusion of the artery.

Secretin was injected intravenously at a slow rate in two doses of 30 milligrams each, given at a 5 minute interval. The ligation of the pancreatic duct was done with care so as not to traumatize the pancreas. We found that the main pancreatic artery could be exposed and clamped easily where it branches from the hepatic artery and runs straight caudad in the gastrohepatic ligament. The artery was occluded with a soft rubber-covered bulldog clamp for 15 minutes and, after removing the clamp, we ascertained by palpation and inspection that circulation in the distal portion of the artery was normal again. The animals, with the exception of 3 that died after the operation, were sacrificed between the 2nd and 8th postoperative days.

The results are presented in Table I, which contains the control experiments and in Table II, which shows the results in the 10 dogs in which temporary occlusion of the pancreatic artery was performed in the presence of edema of the pancreas.

Dogs 1, 2, and 3 (Table I) developed an extensive edema of the pancreas following ligation of the main pancreatic duct and subsequent injection of secretin. No arterial occlusion was performed. The animals were sacrificed on the 3rd, 5th, and 6th postoperative days, respectively, and autopsy showed some induration of the pancreas in 1 of the dogs, but otherwise no gross and no microscopic changes of the pancreas. In dogs 4 and 5 the main pancreatic duct was ligated, but no secretin was given and no edema appeared. Subsequently, the pancreatic artery was clamped for 15 minutes. These dogs were sacrificed on the 3rd and 6th postoperative days, respectively. One of these dogs showed grossly an indurated pancreas, the other showed only microscopic signs of a beginning cirrhosis of the pancreas. Dog 6 received secretin injection without previous duct ligation and no edema developed. Five minutes after the termination of the secretin injection the pancreatic artery was clamped. The dog was sacrificed on the 5th postoperative day; autopsy revealed no gross abdominal pathology and no microscopic changes in the pancreas. Dog 7 received secretin after ligation of the main pancreatic duct, but no edema developed. Five minutes after the termination of the secretin injection the pancreatic artery was clamped for 15 minutes. The dog was killed 8 days later. Autopsy revealed no gross abdominal pathology and no gross changes in the pancreas. Microscopic examination of several sections of the pancreas revealed a normal gland.

In Table II the results are tabulated according to the degree of pancreatic edema present just before occlusion. In experiments 8 and 9, without ligation of pancreatic ducts, a low grade edema appeared after secretin injection. Dogs 10 to 16 had the ducts ligated and developed pancreatic edema after injection of secretin. In 4 of these dogs only a moderate degree of edema appeared, because relatively small doses of secretin had been administered to 2 dogs and a preparation of secretin of low potency had been given to the other 2 dogs.

TABLE II.—EXPERIMENTAL SERIES

Dog No.	Duct ligation	Secretin injection i. v.	Arterial occlusion (15 minutes)	Edema*	Postoperative day		Gross findings	Histologic findings
					Sacrificed	Died		
8	o	+	+	(+)	2		Some bloody fluid in abdomen. Some fat necroses in pancreas and omentum	Fat necrosis of fat tissue. Superficial pancreatic necrosis
9	o	+	+	(+)		2	Many fat necroses in omentum. Bilateral pneumonia	Fat necrosis of fat tissue
10	+	+**	+	+	5		Some bloody fluid. Some fat necroses in and around pancreas	Fat necrosis of fat tissue
11	+	+**	+	+		4	Some bloody fluid. Some fat necroses around pancreas. Bilateral pneumonia	Edema of the pancreas. Superficial pancreatic necrosis
12	+	+	+	+	6		Some fat necroses in omentum.	Fat necrosis of fat tissue
13	+	+	+	+	6		Some fat necroses in omentum	Fat necrosis of fat tissue
14	+	+	+	++	3		Scattered fat necroses in omentum and mesentery. Middle portion of pancreas discolored, showing fat necroses	Hemorrhagic pancreatitis. Fat necrosis of fat tissue
15	+	+	+	+++		2	Acute pancreatitis with diffuse peritonitis	Pancreatic necrosis. Fat necrosis of fat tissue
16	+	+	+	+++	2		Large amount of bloody fluid. Large number of fat necroses in omentum and around pancreas. Edema of pancreas	Fat necrosis in pancreas Edema of pancreas
17	+	o	+	+++	3		Large amount of bloody fluid. Diffuse fat necrosis. Acute hemorrhagic pancreatic necrosis	Pancreatic necrosis. Fat necrosis of fat tissue

*Edema: (+) slight; +moderate; ++marked; +++very marked.
**Single dose of 35 mgm. secretin.

The 3 remaining dogs showed very extensive edema: dog 17 developed very marked edema of the pancreas shortly after ligation of the main and accessory pancreatic ducts, and therefore temporary arterial block was performed without injection of secretin. Dogs 9 and 11 died of pneumonia on the 2nd and 4th postoperative days, respectively, and dog 15 died of pancreatitis and peritonitis on the 2nd postoperative day.

Table II shows, in contrast to Table I, that in every dog some degree of pancreatitis and of fat necrosis existed. The 6 dogs (8 to 13) that had only low grade edema of the pancreas at the time of the arterial occlusion did not show marked generalized changes of the pancreas, but 4 of these dogs had bloody intraperitoneal fluid and all of these animals had fat necroses around the pancreas and in the omentum. Microscopic examination revealed fat necroses in all of these animals and small areas of glandular necrosis in the pancreas of dogs 8 and 11.

All dogs with extensive pancreatic edema at the time of arterial occlusion revealed pronounced changes. Dog 16 had large numbers of fat necroses in the omentum and around the pancreas, and sections revealed extensive areas of fat necrosis in the pancreas and in the peripancreatic fat tissue. The 3 other dogs showed changes that looked like pancreatic necrosis or hemorrhagic pancreatitis with diffuse fat necrosis which, on microscopic examination, proved to be hemorrhagic and necrotizing pancreatitis with extensive fat necrosis.

COMMENT

Since we did not succeed in producing pancreatic necrosis by increasing or prolonging the edema producing administration of secretin, it became apparent that pancreatic necrosis or hemorrhagic pancreatitis is not merely an advanced form or a later stage of pancreatic edema. It seemed probable that an additional factor was responsible. This additional factor was not added by such procedures as obstruc-

tion of lymphatic drainage, obstruction of venous return from an edematous pancreas, or the production of shock in dogs with edema of the pancreas. However, positive results were obtained with the temporary occlusion of the main pancreatic artery, if performed while edema of the pancreas was present. If no edema of the pancreas was present, clamping of the pancreatic artery did not produce pancreatitis. When pancreatic edema was present, clamping of the artery caused pathologic changes in and around the pancreas that were in direct proportion to the degree of the edema, whether the edema was caused by injection of secretin or had developed spontaneously. In case of low grade edema, only fat necroses developed, but in cases with extensive edema all the changes were found that severe forms of pancreatitis can reveal.

We have shown in previous experiments (4) that edema of the pancreas can be produced by vigorous stimulation of the external pancreatic secretion by secretin injection after the main pancreatic duct has been ligated, and we have shown (2) that the intrapancreatic and peripancreatic edema consists of pancreatic juice that has diffused into the connective tissue of the gland. The edema will do little or no damage to the pancreatic gland and will disappear shortly after the secretory stimulus has been discontinued, leaving few or no traces. This process seems to be identical with the clinical picture of "transient pancreatitis."

However, when the arterial supply of the pancreas is interrupted in the presence of pancreatic edema, changes will develop that range from mild forms of intraperitoneal fat necrosis to severe hemorrhagic and necrotizing pancreatitis. The temporary ischemia probably lowers the resistance of the cells to the enzymatic action of the edema fluid, but it is possible that the pancreatic enzymes of the edema fluid might be activated by contact with impaired cells.

Whatever the explanation may be, the important fact is that temporary local ischemia is able to transform a clinically harmless transient edema of the pancreas into a hemorrhagic pancreatic necrosis.

The clinical applications of these experimental observations are:

1. Local vasomotor changes may be responsible for the transition of pancreatic edema into pancreatic necrosis.
2. The extent of local vasomotor changes may determine the degree of pancreatitis.
3. If acute pancreatitis is diagnosed or its presence is suspected, everything should be done to make a presumably present edema disappear and to avoid local ischemia.

To make the edema disappear it seems best to give spasmolytics which will relax the sphincter of Oddi, to prevent any stimulation of the external secretion of the pancreas, and to attempt its active inhibition. There is little we can do to prevent local ischemia except to prevent shock and to avoid medication that has a vasoconstrictor effect in the splanchnic area; administration of papaverine with its vasodilating action may be of value.

Local vasomotor changes are nothing unusual after surgical procedures and this may in part explain the poor results of surgical intervention in acute pancreatitis.

In previous publications (1) impressive therapeutic results were reported with paravertebral block in acute pancreatitis. In the light of the recent experiments it seems suggestive to ascribe these good results partly to local vasodilation produced by blocking the sympathetic innervation to the pancreas.

SUMMARY

Experiments prove that pancreatic edema and acute pancreatitis or pancreatic necrosis are not merely different degrees of the same process but that another pathogenetic factor is necessary to transform one into the other.

In animal experiments transformation of pancreatic edema into pancreatitis or pancreatic necrosis was attained by temporary occlusion of the main pancreatic artery.

The important part which local vasospasm and ischemia may play in the development of clinical cases of acute pancreatitis is discussed and therapeutic measures are recommended.

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SELF CENTERING LORENZ OSTEOTOMY

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THE Lorenz osteotomy has proved one of the most effective methods of treating nonunion of fractures of the neck of the femur, especially in the case of elderly people who could not tolerate some of the more extensive operative interventions.

Careful analysis of a relatively large number of such operations, performed during the last 9 years, has shown that the most common cause of failure has been the displacement of the shaft of the femur either anteriorly or posteriorly to the stump of the neck and head against which the shaft must impinge for stability on weight bearing. The "self centering" Lorenz osteotomy has been devised to minimize this danger.

The principle of the "self centering" osteotomy is the "V" cutting of the femur at just above the superior border of the lesser trochanter, so that a trough is made from the lateral to the medial aspect of the femur with the central portion of the "V" about ½ inch lower than the sides. The "V" cut then tends to center the shaft of the femur under the head, and there is far less tendency for it to gravitate either anteriorly or posteriorly to the desired position. As is already well known to those who have done the Lorenz osteotomy, the shaft must be pushed medially so that it comes to rest directly under the head.

The direct lateral approach has the advantage of less surgical trauma and of speed of procedure. When excellent x-ray facilities are available for control, this approach is the preferred method especially in thin people. When x-ray facilities are not available, and in obese women, it has been the author's experience that the "hockey stick" incision, with cutting of the fascia lata at the inferior portion of the

From the Fracture Service, Cook County Hospital.

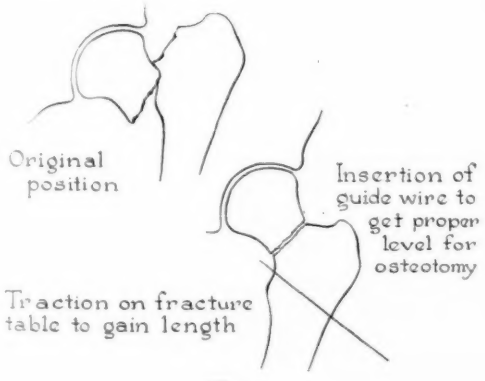

Fig. 1.

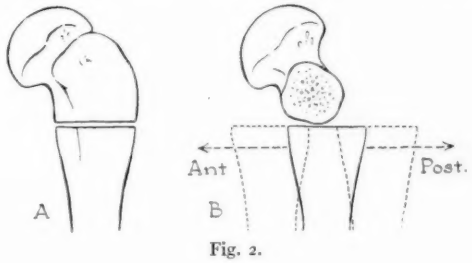

Fig. 2.

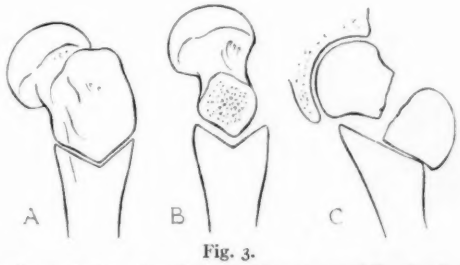

Fig. 3.

Fig. 1. It is desired that the osteotomy be done just above the superior margin of the lesser trochanter. For this reason a Kirschner wire should be placed, under x-ray control, at the desired angle and location for the osteotomy.

Fig. 2. In the original Lorenz osteotomy, a transverse cut was made as illustrated in Figure A, with a resulting possibility of the shaft gravitating either forward or backward from the desired central position, as illustrated in Figure B.

Fig. 3. By producing a forked osteotomy, Figure A, the shaft tends to seek and maintain a central position under the head and neck, Figure B, because of the slanting sides of the osteotomy which constantly tend to "self center" the shaft of the femur. The anteroposterior position of the resulting osteotomy should be as shown in Figure C.

incision and muscle plane dissection between the rectus femoris and extensor fascia femoris, has been more advantageous. By opening the capsule through a longitudinal incision, direct visual control is possible of the fracture site, the location of the osteotomy, and the final position of the shaft of the femur under the neck of the femur.

In doing the osteotomy, a longitudinal muscle splitting of the vastus lateralis can be carried out and the lateral aspect of the femur exposed. In the author's experience this procedure has been most advantageous, as it can be rapidly done and the occasional bleeder can be readily isolated and ligated. Others prefer to locate the posterior margin of the vastus lateralis and reflect the entire muscle anteriorly, thereby exposing the femur at the desired level for the osteotomy. Either method is satisfactory.

Postoperatively, the patient must be placed with the limb operated upon in wide abduction to maintain the shaft of the femur under the head. A spica cast to the toes on the side operated upon and to the knee on the other side is the best method of immobilization. In the application of the cast, care must be taken that too much strain is not placed on the medial side of the knee joint when abduction of the femur is sought, otherwise an undesirable genu valgus results.

It has been found most advantageous to maintain immobilization in a cast for 8 weeks and then to place the limb in skin traction with five pounds of weight, and each day bring the leg a little more into adduction. When the extremity reaches a parallel position to the long axis of the body, the traction is removed and the patient is gotten up on crutches with light weightbearing.

In the average case, ambulation with a cane and with minimal discomfort is possible in about 4 to 6 months after operation has been carried out.

FACTORS INFLUENCING MORTALITY FROM ACUTE PERFORATED PEPTIC ULCERS

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Cincinnati, Ohio

ALTHOUGH considerable strides have been made in the treatment of perforated peptic ulcer since the first successful closure reported in 1892 by Heussner, this condition remains one of the most serious of the common emergencies of abdominal surgery. Recent reports indicate a marked reduction in operative mortality rates from the series reported in 1940 by DeBakey, with 18.2 per cent mortality, to the more recent figures of Graham, 6.4 per cent, Fallis, 8.3 per cent, and Baritell, 1.1 per cent.

Our mortality statistics are not presented as representing the ultimate goal of therapy. Most of our group of patients are from the lower strata of society and enter the hospital in poor nutritional and physical condition. This type of patient taxes therapeutic measures to the utmost.

The present study comprises 336 cases of acute perforated peptic ulcer seen at the Cincinnati General Hospital during the 12 year period 1935-1946 inclusive, and treated by the resident surgical staff (Fig. 1). In routine care at this clinic simple closure of the ulcer, closure of the abdomen with wire, and careful preoperative and postoperative control of fluid balance have been emphasized. The general mortality by 3 year periods has shown a progressive decline from 31 per cent in the period 1935-1937 to 11 per cent for the period 1944-1946. The operative mortality has been reduced from 21 per cent to 10.7 per cent in the same time (Fig. 2).

One of the most important factors affecting the operative mortality in perforated ulcer is the time elapsing before closure of the perforation (Table I). Comparison of our series with that of DeBakey shows that 87.9 per cent of our patients were operated upon within the first 12 hours as compared with 81.85 of his cases. DeBakey reported that the mortality rate increased from 14.6 per cent in patients operated upon within the first 12 hours to 42.6 per cent of those in the 12 to 24 hour group, and reached 61.5 per cent in patients in whom over 24 hours had elapsed. Our mortality statistics for the period 1935 to 1941 are substantially the same as DeBakey's, but in the last 3 year period (1944-1946) we have experienced a drop to 6.4 per cent mortality among patients undergoing operation within the first 12 hours.

The age of the patient also markedly influences the mortality rate (Fig. 3). More than three times as many deaths occur in the 50 to 59 year age as in the 20 to 29 year old group. Comparison of our series with that of DeBakey shows a striking similarity in the mortality curve, deviating only at the 70 to 79 year group. Tabulation reveals that 41.5 per cent or less than half of our patients have been under 40 years of age, as compared with 55.1 per cent of DeBakey's series (Fig. 4). We have further noted in comparing our patients of the 20 to 29 year age group with the patients over 50 that 22.5 per cent of the older group were seen more than 24 hours after perforation while in the younger group only 4.5 per cent entered the hospital after 24 hours had elapsed. In our cases the diagnosis has been more often missed or delayed in the older patients, since many of this group enter the hospital late in the course of their illness.

Three adjuvants to routine treatment have been added in the 12 year period covered by this study. These have been: (1) the use of continuous gastric suction, (2) the use of spinal anesthesia, and (3) the introduction of chemotherapy (Fig. 5). Wangensteen suction drainage was introduced in 1935, and since 1938 has been used in 100 per cent of the cases. Spinal

From the Department of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital.
Presented in the Forum on Fundamental Surgical Problems before the Clinical Congress of the American College of Surgeons, September 8–12, 1947.

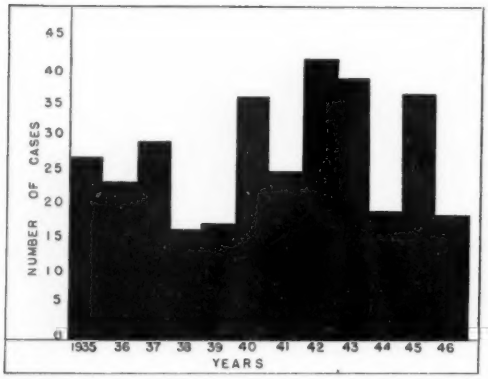

Fig. 1. Number of cases seen per year in period 1935-1946, of total of 336 cases at Cincinnati General Hospital.

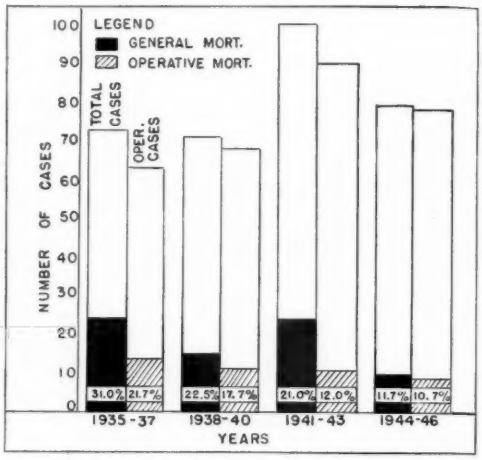

Fig. 2. Comparison of genera and operative mortality rates by 3 year periods, 336 cases seen at Cincinnati General Hospital from 1935 through 1946

anesthesia was also introduced in 1935, and has been employed in varying numbers of cases throughout the 12 year period. We have not been able to demonstrate that the use of spinal anesthesia directly affects the mortality rate nor that respiratory complications have increased or lessened because of its use.

Administration of sulfonamides was begun in 1938, and was gradually increased until 100 per cent of patients with perforated ulcer were receiving this therapy by 1945. In 1945 penicillin was given to 50 per cent of the cases; by 1946 all patients received penicillin and 50 per cent were given sulfadiazine in addition.

The value of chemotherapy in decreasing the incidence of wound infection and subphrenic abscess is clearly demonstrable. Wound infection, which had occurred as frequently as in 30 per cent of the cases (Fig. 6) was reduced to 10 per cent when half of the patients operated upon received penicillin, and was completely eliminated with routine administration of penicillin. The most striking results have been obtained in the group of patients undergoing operation within the first 6 hours after perforation and given chemotherapy. There have been no deaths in this group in the last 3 year period. In the group operated upon within 7 to 12 hours after perforation and given chemotherapy, mortality has been reduced from 21.6 per cent to 10 per cent since the use of sulfonamides, and to 7.7 per cent with the introduction of penicillin. Subphrenic abscess has occurred in 11 patients following closure of gastroduodenal perforation. Eight of these developed subphrenic abscess despite the fact that they were receiving sulfonamide therapy. Since the use of penicillin, there has been no incidence of subphrenic abscess. Analysis of the 73 deaths (Fig. 7) revealed that generalized peritonitis was the cause of death in 46.6 per cent. Shock and respiratory complications each caused 13.3 per cent of the deaths, and cardiac difficulty was responsible in 10.6 per cent. Since peritonitis was determined to be the cause of death over 3 times as often as any other single cause, we believe that the bacterial element in perforated ulcer is a most important factor.

TABLE I.—PERFORATED PEPTIC ULCER—306 PATIENTS OPERATED UPON AT CINCINNATI GENERAL HOSPITAL, 1935–1946

Hours elapsed before closure: comparison with DeBakey

Hours	Number of cases	Per cent	DeBakey
0 to 6	141	46.08	50.83
6 to 12	128	41.83	31.02
12 to 18	15	4.9	3.93
18 to 24	8	2.59	1.43
Over 24	14	4.58	13.66
Total cases	306		

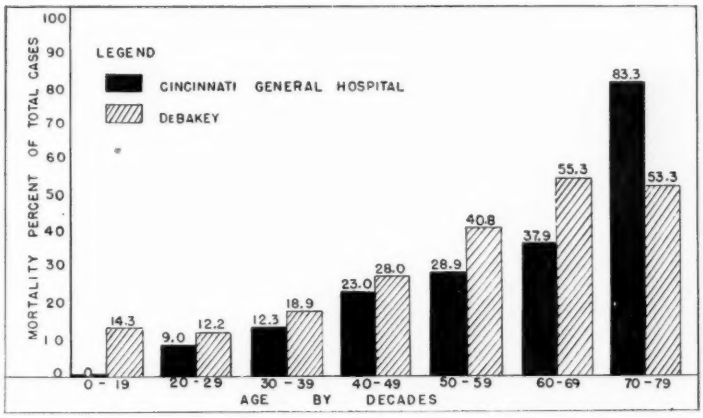

Fig. 3. Mortality rate according to age; comparison with DeBakey.

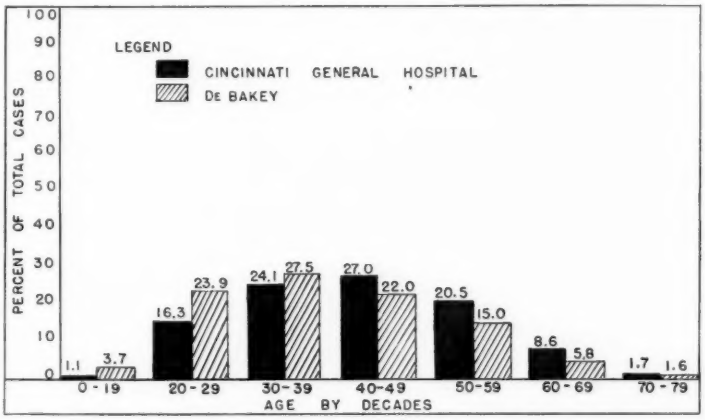

Fig. 4. Age incidence compared with series reported by DeBakey.

Eighty-seven per cent of the patients seen gave a history of previous epigastric distress. Seventy per cent of those with epigastric symptoms gave a history of over 6 months' duration. In our study there were 10 reperforations, an incidence of 2.9 per cent. Nine of these were seen in the first 6 hours. One reperforation was fatal.

Thirteen cases were not recognized as perforated ulcer on admission of patient to the hospital and diagnosis was made on the medical or the psychiatric services. Twelve of these had had ulcer perforated for longer than 24 hours. In 4.5 per cent of the cases, positive diagnosis could not be made. One of the causes for delaying diagnosis was gradual onset of symptoms. Five per cent of our patients had a gradual onset of abdominal pain. In an additional 5 per cent, abdominal pain was noted to occur most markedly in the right lower quadrant.

Vomiting occurred in 47 per cent of the series following perforation; 24 per cent experienced vomiting one time, and 23 per cent vomited more than once. It has often been said that patients with perforated ulcers do not vomit. This has not been true of almost one-half of our cases. It seems likely that the

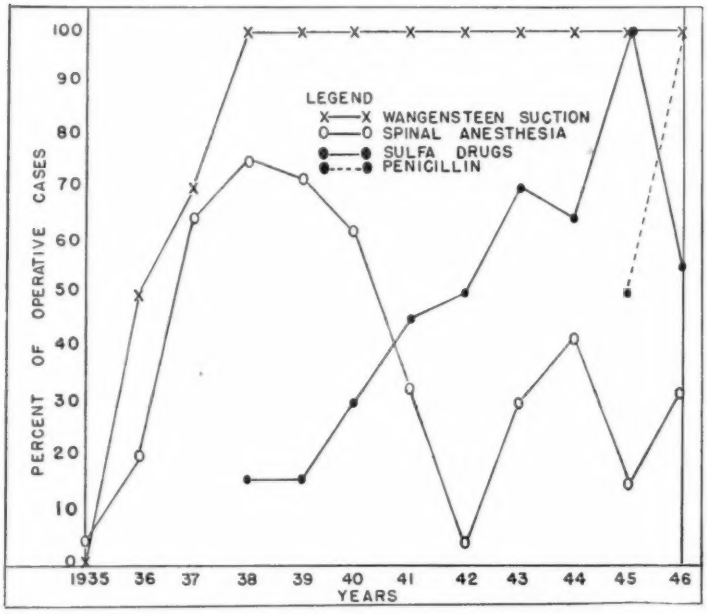

Fig. 5. Percentage of cases receiving Wangensteen suction drainage, spinal anesthesia, sulfonamide drugs, and penicillin.

amount of material in the stomach at the time of perforation determines the amount of vomiting.

Graham found that the white count is usually elevated, and in his series there was only one instance in which the white count was below 5,000. In 4 per cent of our series the white count was below 4,000, in 27 per cent it was between 5,000 and 10,000, in 33 per cent between 10,000 and 15,000, and in 35 per cent above 15,000. Sixty per cent of our cases had a white count of more than 10,000. Temperature on admission to the hospital was less than 99 in 53 per cent of the cases, in 25 per cent it was between 99 and 100, and in 22 per cent it was over 100.

Free air in the peritoneal cavity was demonstrated roentgenologically in 66 per cent of the cases. Abdominal findings were described as board-like or markedly spastic in 68 per cent of the cases. Nineteen per cent had increased abdominal spasm; and distention was not uncommonly seen in cases in which perforation had been present over 24 hours. Hypoactive peristalsis was recorded in only 12 per cent of the cases.

The location of perforation was near the outlet of the stomach in 84.7 per cent of the cases (duodenal 56.8 per cent and pyloric 27.9 per cent). Five and three-tenths per cent were gastric and an additional 1.4 per cent occurred on the posterior surface of the stomach. In the remaining 8.6 per cent the location was not reported. The most frequent location of perforation, i.e. near the pylorus, had apparently not been realized by all of the operators, judging by the length of some incisions. Shorter incisions in certain instances might have reduced the incidence of wound infection and evisceration.

Simple closure of the ulcer consisted of laying three or four Lembert sutures of silk through the ulcer bed, closing the ulcer and placing a tag of omentum in the long ends of the sutures and tying it down over the suture line. In cases in which the ulcer could not be easily closed a fold of stomach has been drawn down over the perforation. No cases of py-

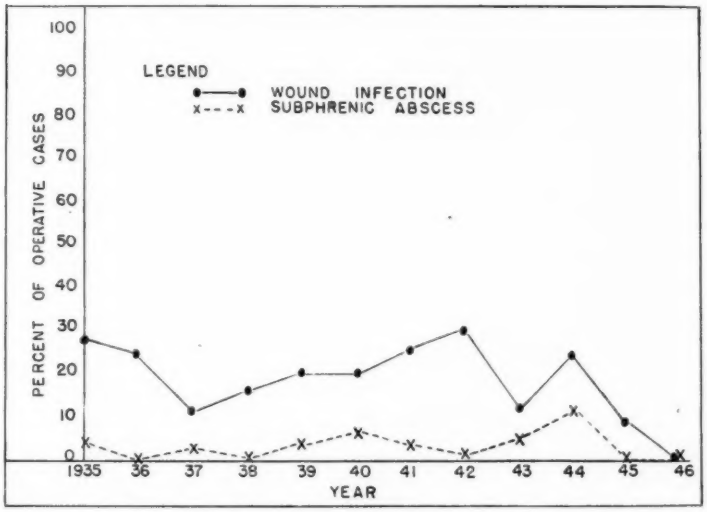

Fig. 6. Incidence of subphrenic abscess and wound infection.

loric stenosis were noted. Two cases of duodenal fistula, one of which communicated with a subphrenic abscess, were encountered.

Wound closure was carried out by through and through silver wire plus catgut in the peritoneum and fascia in 60 per cent of the cases. Thirty per cent were closed with through and through silver or steel wire with no peritoneal closure. Four per cent were closed in layers with catgut with silkworm gut stays, and 4 per cent were closed in layers with silk.

Wound evisceration has been the chief incentive for wire closure. In 8 instances evisceration requiring secondary closure occurred. Silver wire had been used in 5 of these. Three eviscerations were associated with coughing, and in each instance the wires broke. The cause was attributed to finer grades of silver wire being used at that time than is ordinarily recommended and steel wires have been more extensively adopted since. Evisceration occurred in one individual in whom the peritoneum had been closed in addition to the silver wires. In the other case omentum herniated between the wires. In 2 cases in which closure had been made with catgut and silkworm gut stays the sutures broke. In the eighth case closure had been made in layers with silk. Three patients died after evisceration.

In the last 6 years, positive cultures were obtained at operation in 29.8 per cent of the cases. In one-fourth of this group the outcome was fatal. On the other hand, seven-eighths of all fatal cases for this period had had positive cultures at operation. Other writers have reported an incidence of positive cultures at operation varying between 0 and 93 per cent. Brütt reported 74 per cent positive cultures in cases undergoing operation within 6 to 12 hours, and 93 per cent in cases in the group over 12 hours. The fact that an average of 23 per cent of cases in this series developed wound infection prior to the use of penicillin although positive peritoneal cultures were obtained in only 29.8 per cent of the cases indicates that the organisms are of a very virulent nature or that our present culture methods are not adequate. Analysis of culture reports reveals that 49 per cent of the positive cultures contained more than one organism. Streptococcus was found in 75.47 per cent of the cultures; 23 per cent of these were of the hemolytic type. Staphylococcus was found in 32 per cent, Bacillus coli in 18.8 per cent, and Aerobactor aerogenes in 15 per cent.

Shock associated with acute perforated ulcers has been a subject of considerable discussion. Soutter studying 335 cases found pro-

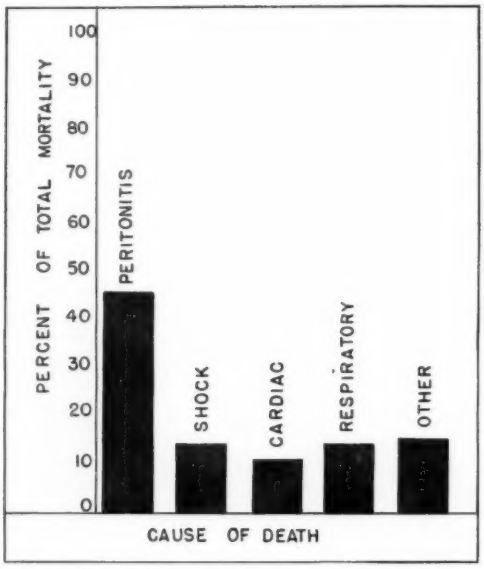

Fig. 7. Cause of death—73 cases.

found shock in only 3 instances and mild shock in 6 per cent. He attributed early shock to associated hemorrhage and late shock to peritonitis. Graham emphasized the nutritional and biochemical imbalance associated with shock as being responsible for the serious state of these patients. Blood pressure has been selected as the most constant single criterion of shock. In this series there were 25 patients or 7.4 per cent with blood pressure below 100 millimeters systolic on admission. In 14 or over half of these the ulcer had been perforated less than 12 hours. Three of the patients with perforation of less than 12 hours' duration succumbed to shock and were not operated upon. One of these patients was a female, age 52, with a previously perforated gastric ulcer, who was in shock on admission 4 hours after perforation. She had associated gastric hemorrhage and expired. The 2 other cases were 7 and 12 hours post perforation respectively. There was no evidence of gastrointestinal hemorrhage, but in spite of therapy with intravenous blood both expired.

Ten of the patients in shock on admission less than 12 hours after perforation were operated upon, with 8 recoveries. None of the 11 patients entering more than 12 hours after perforation with blood pressures under 100 millimeters systolic survived. Five of these underwent operation.

Four cases with adequate blood pressure at time of operation died within 36 hours after operation in shock-like condition. They had been closed 2½, 7½, 9, and 17 hours respectively following perforation. Three of these had positive cultures in the peritoneal fluid. In another instance a patient who had an ulcer perforated for 5½ hours was given a spinal anesthetic, following which the blood pressure fell and he succumbed.

There have been 38 patients who had perforations for over 24 hours before admission to the hospital. Fourteen of these who had adequate blood pressures were operated upon. Four survived, giving a mortality of 71 per cent. Twenty-four patients were treated without operation, 16 of whom died, a nonoperative mortality of 66 per cent. In our hands nothing has been gained by operation after 24 hours postperforation.

Thirteen of the patients in this study have been women, an incidence of 3.8 per cent, as compared with 1.9 per cent in DeBakey's Charity Hospital series and 7.7 in his collected series. Of the 13, 11 were over 40 years of age. Only 6 of the women were admitted in the first 12 hours postperforation. There were 5 deaths, 4 of which followed perforation for over 24 hours. The occurrence of perforation in women near of after the menopause is in keeping with the work of Sandweiss, who believes that there is a protective mechanism produced by the ovary and the pituitary gland in younger women which lessens the chance of perforation occurring.

Our therapy, although not striking in comparison with the work of others, has shown a steady improvement in survival rate in the 12 year period 1935 to 1946. Analysis of the operative deaths for the last 3 years shows that over half of our patients have entered the hospital more than 6 hours after perforation had occurred. In order to give a clearer picture of the type of patient seen at the Cincinnati General Hospital, an important influencing factor on our mortality statistics, the 9 fatal cases of the last 3 years are briefly summarized.

CASE 1. White female, aged 67 years. This patient was admitted 9 hours after perforation, and air was demonstrated under the diaphragm on roentgenological examination. She was treated with 3 units of blood and 2 of plasma. A large perforation of the greater curvature of the stomach was closed under cyclopropane anesthesia 16 hours after perforation. Streptococcus nonhemolyticus and Staphlococcus hemolyticus were cultured from the peritoneal cavity. Despite administration of 20,000 units of penicillin every 3 hours the patient died within 48 hours. Necropsy revealed (1) acute fibrinous peritonitis, and (2) acute lobular pneumonia.

CASE 2. White female, aged 76 years. This patient entered the hospital 48 hours after onset of symptoms, and received intravenous fluid therapy for 2½ hours. A small perforation of the anterior duodenum was closed under cyclopropane anesthesia, and a peritoneal culture was taken which revealed a yeast. The patient died on the 18th postoperative day. Necropsy showed (1) peritonitis, and (2) thrombosis of mesenteric vessels with small and large bowel infarction.

CASE 3. Colored male, aged 36 years. This patient had far advanced tuberculosis. A large perforation of the lesser curvature of the stomach was closed 12 hours after its occurrence. Although the patient received penicillin and sulfadiazine, his postoperative course was very stormy, and he died on the 14th hospital day. Autopsy revealed a perforated duodenal ulcer below the one which had been closed.

CASE 4. Colored male, aged 45 years. A large perforation of the pylorus of at least 48 hours' duration on admission was closed under local anesthesia despite the low blood pressure of the patient. A streptococcus and Bacillus coli were revealed in cultures obtained at operation. Despite supportive therapy, including 15,000 units of penicillin every 3 hours, 3 units of blood, and oxygen by catheter, the patient remained confused and disoriented and died within 36 hours.

CASE 5. White male, aged 50 years. A small perforation of the anterior duodenum was closed 9½ hours after occurrence under cyclopropane anesthesia. A streptococcus was cultured from the peritoneal cavity. He was given sulfadiazine 5 grams daily until the third day when he received in addition penicillin 20,000 units every 3 hours. He developed delirium tremens on the 4th hospital day, and died on the 5th hospital day of bronchopneumonia.

CASE 6. White male alcoholic, aged 55 years. This patient was admitted to the hospital with a fractured femur. He developed a large anterior duodenal perforation which was closed 17 hours after occurrence. A Bacillus aerogenes was cultured from the peritoneum. In spite of two units of blood and two units of plasma this patient went into shock and did not recover.

Case 7. White female, aged 58 years. This patient entered the hospital 12 hours after onset of symptoms and was given one unit of blood on admission. A large perforation of the pylorus was closed under local anesthesia 6½ hours later. Staphlococcus aureus hemolyticus, Streptococcus viridans, and Streptococcus nonhemolyticus were cultured from the peritoneum. She received 5 grams of sulfadiazine daily, but died on her fourth hospital day. Autopsy revealed generalized peritonitis.

CASE 8. Colored male, aged 58 years. This patient entered the hospital 32 hours post perforation. After 4½ hours of therapy, including blood transfusion, a small anterior duodenal perforation was closed under cyclopropane anesthesia. Streptococcus viridans was cultured from the peritoneum. The patient received sulfadiazine 5 grams daily for the first 7 days, and penicillin, 20,000 units every 3 hours, was added thereafter. He died on his 11th postoperative day. Necropsy revealed generalized peritonitis, subhepatic abscess, and pulmonary infarct.

CASE 9. White male, aged 33 years. A small perforation of the anterior duodenum was closed under cyclopropane anesthesia 7 hours after duodenal rupture. The patient developed delirium tremens on his second postoperative day. He received 5 grams of sulfadiazine daily for 10 days. He insisted on leaving the hospital on the 24th hospital day while still running a febrile course, but soon returned and succumbed on his 62nd postoperative day. Autopsy revealed multiple gastric ulcers, multiple liver abscesses, subphrenic abscess, peritonitis, and portal thrombosis.

SUMMARY

A report of 336 cases of acute gastroduodenal perforation in a large general hospital has been made. The mortality rate has shown a progressive decline from 21 per cent to 10.7 per cent in the 12 year period 1935 to 1946. Under combined penicillin and sulfadiazine therapy, the mortality rate has been dropped to 0 per cent in patients treated in the first 6 hours and to 7.5 per cent in patients treated between 6 and 12 hours.

Introduction of chemotherapy with both penicillin and sulfadiazine at the time of diagnosis is advocated, since bacterial infection is a most important factor in mortality. Eighty-eight per cent of fatal cases had a positive culture from the peritoneal cavity. There was 25 per cent mortality among patients from whom a positive culture was obtained at operation. Seventy-five per cent of the positive peritoneal cultures contained a streptococcus. Generalized peritonitis was the greatest single cause of death.

Efforts should be directed at early diagnosis, especially in women and in older people. In such patients symptoms are not so dramatic

and apparent as in the younger group. Although death from postoperative shock has been rare in our series, it continues to be a factor, and all patients should receive adequate preoperative fluids and antishock therapy.

Perforated gastroduodenal ulcers of over 24 hours' duration have done poorly in our hands with or without operation.

CONCLUSIONS

Early diagnosis and prompt surgical intervention with supportive chemotherapy are the most important factors involved in the successful treatment of acute perforated gastroduodenal ulcer.

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INTRAVENOUS, SUBCUTANEOUS AND RAPID INTRAMUSCULAR INFUSIONS OF "PROTEIN HYDROLYSATE"

JACOB JOSEPH WEINSTEIN, M.D., Washington, District of Columbia

A RATHER exhaustive investigation of parenteral bovine protein hydrolysate is being conducted. Since the maintenance of protein nutrition in surgical patients requiring parenteral feeding demands intensive therapy with large daily injections, we have attempted to analyze the effectiveness of intravenous, subcutaneous, and rapid intramuscular infusions of this protein hydrolysate. The study represents clinical as well as experimental experiences with parenteral infusions; further, the advantages and difficulties of the routes are discussed.

The major objectives of this study were: (1) to determine with intravenous infusions, the reaction incidence, the types of reactions, the average amount injected, the average rate of injection, the toxicities, and the local difficulties such as thrombosis, phlebitis, etc.; (2) to determine the effect on the blood and urine of infusions of 1000 cubic centimeters of protein hydrolysate in 1 hour; (3) to determine the plausibility of repeated subcutaneous infusions of 1000 cubic centimeters of protein hydrolysate in the thighs, the effect on the blood, on the legs, and the rate of absorption as determined with the use of phenolsulfonphthalein excretion as an indicator; (4) to determine the feasibility of rapid intramuscular injections of 1000 cubic centimeters of protein hydrolysate into the vastus lateralis of the thighs, the effect on the blood, on the legs, the reaction of the tissues and the absorption rate as calculated by the use of phenolsulfonphthalein excretion as an indicator.

These studies were all conducted on preoperative and postoperative surgical patients on the wards at the Gallinger Municipal Hospital, Washington, D.C. The variables were controlled as well as was possible with the physical establishment available. All of the infusions and chemical analyses were performed by the author and a technician (George F. Lane).

From the Department of Surgery of the George Washington University, School of Medicine and the Surgical Department of the Gallinger Municipal Hospital, Washington, D.C.

Presented in The Forum on Fundamental Surgical Problems before the Clinical Congress of the American College of Surgeons, New York, September 8–12, 1947.

PREPARATION USED

The solution used in the study is 5 per cent parenteral protein hydrolysate in distilled water. The source of protein is bovine blood and is collected under sanitary conditions, processed, and hydrolyzed by means of a pancreatic enzyme preparation. The hydrolysate is then treated to remove harmful and undesirable constituents and diluted to the desired concentration. Filled sealed bottles of the solution are sterilized by autoclaving and packaged in 500 or 1000 cubic centimeter containers. The finished product is a light amber colored solution, containing:

Total solids	5.0 grams per 100 c.c.
Total nitrogen	0.55 gram per 100 c.c.
Ammonia nitrogen	0.015 gram per 100 c.c.
Alpha-amino nitrogen (approximately 50% of the total nitrogen)	0.275 gram per 100 c.c.
Sodium chloride	0.30 gram per 100 c.c. (approximately)
*p*H	6.20—6.40

Chemical analyses of protein hydrolysate reveal the following amino acids and their percentages:

Arginine	4.91	Lysine	6.10
Aspartic acid	4.26	Methionine	1.06
Cystine	1.15	Phenylalanine	3.30
Glutamic acid	10.34	Threonine	6.00
Histidine	1.93	Tryptophane	1.42
Leucine	7.25	Valine	6.15
Isoleucine	3.94		

Each manufactured lot of protein hydrolysate solution is subjected to control procedures to show that it is sterile, nonpyrogenic, free of vasomotor substances, free of unhydrolyzed protein, and that it may serve as an adequate source of parenteral nitrogen.

METHODS

1. Twenty-four hour urine specimens were collected in receptacles containing toluol to

prevent fermentation and were not pooled, but analyzed immediately after collection. Fractional urines studied were kept in individual containers, chemically studied separately, and the total 24 hour results were computed by the addition of the individual figures.

2. Co-operative preoperative or convalescent surgical patients were used for the tolerance studies. They had no recognizable metabolic diseases and were not afflicted with ravages of serious surgical procedures or medical diseases (nephritis, hepatic diseases, nutritional deficiencies, etc.).

3. All blood samples were drawn from the opposite arm used for intravenous infusions into test tubes containing the anticoagulant heparin. These were not stored for longer than 12 hours at 4 degrees to 6 degrees centigrade before chemical analysis.

4. The total nitrogen and nonprotein nitrogen of the urine were obtained by Kjeldahl digestion, distillation, and titration with .015 normal hydrochloric acid (13). Urea estimations were performed by digestion and nesslerization of the filtrate (13). All 24 hour urines were analyzed for total creatinine as a check against faulty collection of specimens. The creatinine output is rather constant under normal circumstances at a level of 0.9 to 1.3 grams per 100 cubic centimeters (13). Amino acid levels of blood and urine were estimated in milligrams by the Folin colorimetric method (2).

5. Control studies with phenolsulfonphthalein were conducted on all patients on whom the rate of excretion of this drug was used as an estimate of protein hydrolysate absorption, when given either by subcutaneous or intramuscular route. The control or normal test was executed thusly: Each patient drank 1000 cubic centimeters of water rather than the conventional 500 cubic centimeters so as to keep the fluid intake equal to the amount to be injected. After the fluid intake, 1 cubic centimeter containing 0.6 gram of phenolsulfonphthalein was injected intramuscularly. Urine specimens were obtained at 1 hour and 10 minutes, 2 hours and 10 minutes, and 3 hours and 10 minutes after the intramuscular injection, and the percentage of dye excreted was calculated by colorimetric comparison with known standards (3).

6. The absorption test with protein hydrolysate to which 0.6 gram of phenolsulfonphthalein is added was performed in the following manner: The day after the control study, the same patients were infused either subcutaneously in 3½ hours or intramuscularly in 30 minutes with 1000 cubic centimeters of protein hydrolysate containing 0.6 gram of phenolsulfonphthalein. Urine specimens were collected at designated intervals, the percentage of dye excreted was obtained by colorimetric comparison, and these figures were then compared with the corresponding control values of excretion. The percentage excretion of normal for this particular patient implies the rate of removal of the dye with the protein hydrolysate from the tissues and its appearance in the urine; thus giving an approximate estimate of the rate of absorption from tissues of the solution containing the phenolsulfonphthalein.

7. Biopsy of muscle (vastus lateralis) is described to reveal the reaction of this tissue to repeated infusions of protein hydrolysate solution.

INTRAVENOUS ADMINISTRATION

An overall reaction incidence of 0.72 per cent was found in two thousand and three (2003) intravenous infusions of 1000 cubic centimeters each in 320 preoperative and postoperative surgical patients.

The types of cases in which the solution was administered frequently represented the more ill surgical patients for it is this group which requires parenteral protein feeding. Some of the surgical diseases included in the group studied are listed for review: ruptured appendicitis with diffuse peritonitis, subtotal gastrectomy and anastomosis for duodenal ulcer or gastric carcinoma, chronic cholecystitis and cholecystectomy, multiple perforations of the intestine after gunshot or stab wounds of the abdomen, perforated peptic ulcers with closure, intestinal fistulas, carcinoma of rectum with combined abdominoperineal resection, essential hypertension and thoracolumbar sympathectomy and splanchnicectomy, and others.

The average amount injected intravenously by gravity at each infusion was 1000 cubic

centimeters, and the usual time required for this quantity was 1 or 1½ hours; thus a rate of 14 to 17 cubic centimeters per minute. Three thousand cubic centimeters per day were administered by continuous drip into the saphenous vein for 7 days to a patient with a small bowel fistula. Hence the largest single injection in the study is 21,000 cubic centimeters. There was no ascending thrombosis or phlebitis in this case. The largest quantity given to a single patient was 42,000 cubic centimeters in 14 days. Many other patients received large amounts for adequate protein therapy, for nitrogen balance in patients on parenteral feeding alone requires full and adequate dosage.

Fifteen reactions were found in the entire study. Three of these, or 0.14 per cent, were characterized by flushing, warmth, nausea, and forcible vomiting, and were labelled "systemic reactions." Ten, or 0.49 per cent, were typical "pyrogenic reactions" which manifested themselves as chills, pyrexia, and tachycardia. Two "allergic reactions" were noted in the same patient; thus an incidence for this type of 0.16 per cent. Of particular interest are the systemic reactions. The first two of these were the first reactions experienced in the entire study and occurred with the first batch of material investigated clinically. The third systemic reaction was noted 6 years after the above mentioned and was in a patient who had had a colon resection. He was receiving 3000 cubic centimeters of protein hydrolysate daily as part of a nitrogen balance study. The reaction occurred on the third day of the study with an infusion of hydrolysate which was being injected at an approximate rate of 15 cubic centimeters per minute. All of the manifestations were abated within 15 minutes after discontinuance of the infusion, but recurred after the infusion of 100 cubic centimeters at the original rate. No subsequent reaction developed when the remainder of the solution (500 c.c.) was infused at 8 cubic centimeters per minute. A sample of the solution causing the reaction was found to be sterile and contained only 50 per cent alpha amino nitrogen. The same patient received 13,000 cubic centimeters of the protein hydrolysate from the same batch causing the reaction and no untoward manifestations were recorded.

In lieu of the recent observations of Hoffman, Kozoll, and Osgood, of Smyth, Lasichak, and Levey; and of our recent observations (11) with rapid intravenous infusions of protein hydrolysate, a blood amino acid level determination at the time of vomiting in the aforementioned reaction may have yielded significant data.

Both allergic reactions developed in the same case. The symptoms were puffed eye-lids, large superficial wheals and shortness of breath after the receiving of 200 cubic centimeters at 15 cubic centimeters per minute on subsequent days. Past history of the patient elicited allergies to milk as a child, diarrhea or hives when she consumes chocolate, and the same type of allergic reaction to "amigen" 5 months previously after 4 days of infusions of this latter preparation. Skin tests in this patient with protein hydrolysate solution produced a large allergic wheal. If patients can become sensitized to enzymatic hydrolysates of casein or blood, it might prove a point of prevention to question all patients who are to receive intravenous infusions of hydrolysates as to whether they have had any previous infusion of protein digests, and as to the development of any allergic reactions. Further, skin testing before infusions on patients who have received hydrolysates would perhaps screen out sensitive individuals.

Since all of the intravenous infusions of protein hydrolysate reported in this entire study were given by the author or a technician, we both had an excellent opportunity to observe the local manifestations. No acute ascending thrombophlebitis or ascending thrombosis was found in any case receiving 1000 cubic centimeters of hydrolysate solution in 1 or 1½ hours, even though repeated infusions were given in either antecubital vein on subsequent days. Local thromboses were found in the veins at the site of repeated injections and infusions. It is the impression of this observer that thrombosis is no more frequent with hydrolysate solution than with similar infusions of 5 per cent dextrose solutions. Much of the local vein reaction can be diminished if the following procedures are

TABLE I.—AVERAGE BLOOD AMINO ACID LEVELS, DIFFERENCES, AND PERCENTAGE OF NORMAL CHANGE FOR TEN CASES RECEIVING 1000 C.C. OF PROTEIN HYDROLYSATE INTRAVENOUSLY IN ONE HOUR

	Amino acid	Difference	Normal change—above normal Per cent	Differences in per cent of normal change
Normal level mgm/100 c.c.	6.5			
500 c.c.—½ hour	7.9	+1.4	21.7	+21.7
1000 c.c.—1 hour	9.1	+2.6	42.2	+20.5
After ½ hour	8.6	+2.1	34.5	— 7.7
After 1 hour	7.66	+1.16	21.5	—13
After 1½ hours	7.06	+0.56	12.5	— 9
After 2 hours	6.77	+0.2	8.0	— 4.5

conducted: (1) select a smaller needle than the caliber of the vein to be used for infusions; (2) execute the venipuncture by a sharp clean puncture through the anterior wall of the vein without damage to the opposite or posterior wall; (3) insert the needle well into the lumen of the vein; (4) avoid undue movement of the needle in the vein during infusion by adequate fixation of the needle, adaptor, tubing and the extremity used; and (5) avoid long continued infusions in the same vein with a single venipuncture. The hazards of prolonged intravenous infusions are related in the following experience. A patient had received four individual infusions of 1000 cubic centimeters each of protein hydrolysate in the right arm at an approximate rate of 1½ hours. Another 1000 cubic centimeters of hydrolysate was inadvertently given slowly over a 5 hour period in the left arm. That night the patient noticed severe pain and soreness in the upper left arm and at the site of the injection in the antecubital fossa. Examination the next morning revealed complete thrombosis of the medial superficial vein of the upper arm extending from the antecubital fossa to the axilla. The skin adjacent to the vein showed inflammation; the entire vein was exquisitely tender to palpation and movement of the arm produced discomfort to the patient. Four days of compressing were required to alleviate the manifestations. Hence, because the discomfort was too great, it was not feasible to use the left arm for further infusions during the patient's hospital stay. The life of available accessible veins in the arm of patients on intravenous feeding may be prolonged by the plan of starting well down on the forearm for the first infusions and then gradually ascending to the antecubital fossa with the repeated injections.

Few patients who have received 3000 or 4000 cubic centimeters of protein hydrolysate daily as part of an investigation of nitrogen balance have caused us any difficulty with successful venipuncture after numerous intravenous infusions. In a study of parenteral hydrolysates in parenteral nutrition, Koop and associates, report thrombosis as a common occurrence with all preparations used for considerable periods. "The tendency to thrombosis was subject to marked variation between individual patients and in several patients the infusion of hydrolyzed protein had to be stopped for this reason. Venous thrombosis appeared to be the chief limiting factor in parenteral nutrition" (7).

Blood amino acid levels and urine chemical changes with intravenous injection of 1000 c.c. protein hydrolysate in one hour. Ten preoperative or postoperative surgical patients who did not manifest any gross evidence of nutritional deficiency or serious surgical maladies were used for this study. The average serum protein was 6.8 grams per 100 cubic centimeter of serum for the 10 subjects before the infusions. The intravenous injection of 1000 cubic centimeters of hydrolysate was performed in the right arm in the antecubital fossa by gravity in 60 minutes; thus an approximate rate of 17 cubic centimeters per minute. The blood samples were drawn from

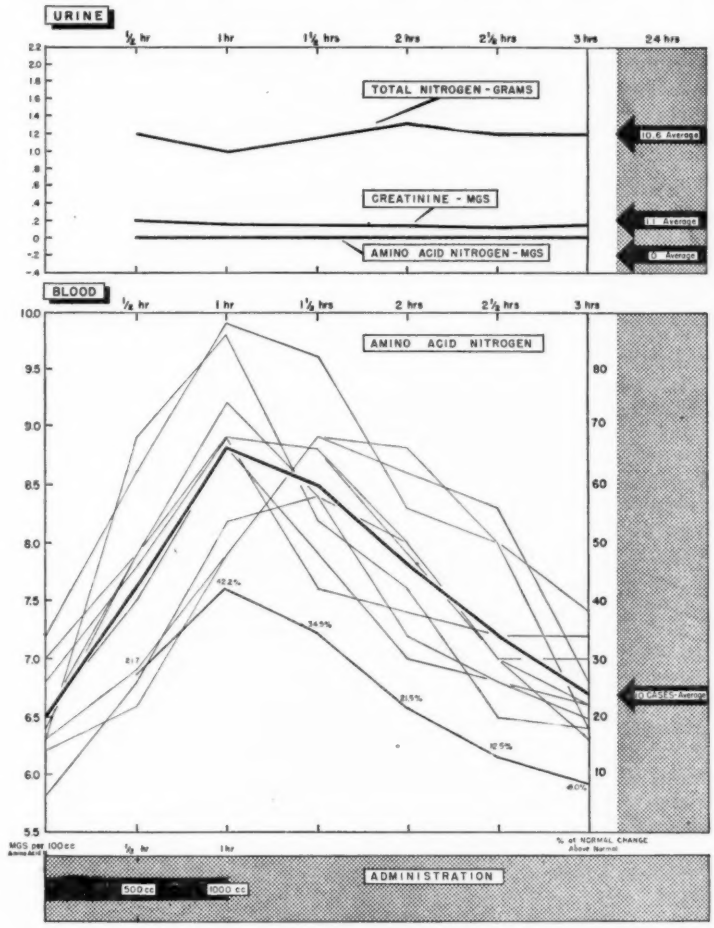

Chart 1. Intravenous protein hydrolysate.

the left or opposite arm before the infusion, after the infusion of 500 cubic centimeters, after the infusion of 1000 cubic centimeters, 30 minutes, 1 hour, 1½, and 2 hours after completion of the intravenous injection. The urine samples were collected, when possible, at intervals corresponding to the drawing of blood and throughout the 24 hour period. Thus a total 24 hour urine was obtained fractionally.

The average blood amino acid levels, the differences, and percentage of normal change for the ten cases are shown in Table I.

The amino acid nitrogen rose 21.7 per cent above normal or 1.4 milligrams per 100 cubic centimeters of serum after the infusion of 500 cubic centimeters of protein hydrolysate. The maximum individual rise for this period was to 8.9 milligrams or a 2.9 milligram rise above the normal level for this period. The least rise was 0.9 milligram. The average blood amino acid rise after the injection of the latter 500 cubic centimeters was 1.3 milligrams or 20.5 per cent above the preceding level. Hence the average total rise with the injection of 1000 cubic centimeters of protein hydrolysate is

42.2 per cent above normal or a 2.6 milligram rise from the base reading. These figures indicate a higher percentage rise for the first 500 cubic centimeters as compared to the second. The difference may be explained by the fact that blood amino acids are being removed throughout the period of injection, and that the rate of metabolism may somewhat parallel the level of amino acids in the blood. During the first half hour after the end of the 1000 cubic centimeter infusion, 7.7 per cent decrease in amino acids is noted and a 13 per cent removal occurs in the following 30 minutes. Therefore 20.7 per cent of the circulating amino acids are utilized in the first postinfusion hour. The following 1 hour period showed a 13.5 per cent decrease in amino acid level. Survey of the individual cases reveals a close correspondence to the average figures presented. Finally, 2 hours is the usual time required for the removal of the major part (81 per cent) of maximum total circulating amino acids resulting from the injection of 1000 cubic centimeters of protein hydrolysate in 1 hour.

Amino acids were not detected in any of the urine samples analyzed. The total urinary nitrogen determinations revealed 24 hour outputs ranging between 9.6 grams and 12.3 grams of nitrogen with an average output of 10.56 grams of nitrogen per day. This figure is well within the range of the average output of convalescing ambulatory surgical patients on a regular hospital diet in our institution. The total creatinine values varied between 1.1 and 1.4 grams and averaged 1.16 grams per 24 hour urine sample—a figure that represents the usual total output for creatinine. This is used as a guide for the correct collection of all urine specimens during the 24 hour study period. The effect of the intravenous administration of 1000 cubic centimeters of protein hydrolysate in 1 hour on the blood amino acid nitrogen and the urinary excretion of nitrogen and amino acids is shown in Chart 1.

No nausea or vomiting was seen in any of the 10 cases with the infusion of 1000 cubic centimeters of protein hydrolysate in 1 hour or at a rate of 16 cubic centimeters to 17 cubic centimeters per minute. Recent observations to be reported show that vomiting occurs with protein hydrolysate when it is given at a rapid rate varying between 50 cubic centimeters per minute and 140 cubic centimeters per minute. The blood amino acid levels at this point are 14 milligrams per 100 cubic centimeters of serum or more (11).

SUBCUTANEOUS ADMINISTRATION

Four hundred and twenty subcutaneous infusions of 1000 cubic centimeters of protein hydrolysate have been infused into 136 patients without any local difficulties or failure of absorption. Twenty-five or 50 cubic centimeters of 1 per cent novocain is added to the solution partially to novocainize the area of injection. Slow, even infusions without undue distention permit the most comfortable and readily absorbed subcutaneous infusions. It is a mistake to overdistend subcutaneous tissues by rapid infusions of protein hydrolysate. The practice of rapidly infusing 200 cubic centimeters or more, stopping the infusion until absorption has taken place and repeating this process four or five times until 1000 cubic centimeters is administered is faulty for it produces local discomfort, pain, delays or prolongs absorption, and increases the incidence of local complications.

In this study the site used for subcutaneous infusions was the anteromedial aspect of both thighs. A 2½ inch, No. 18 or 19 gauge needle is most commonly employed. When feasible, a novocain intradermal wheal is made before insertion of the needle into the subcutaneous tissue. The usual time required for the infusion of 1000 cubic centimeters of protein hydrolysate varies between 2½ and 4 hours. The time factor is influenced by the degree of hydration, the amount of subcutaneous fat, and the age of the patient. Elderly patients who are not too thin seem to absorb the fluid more readily than the average young or middle aged adult. A normal amount of subcutaneous fat aids absorption whereas excessive amounts of soft fat decrease absorption and enhance local complications. It is our common practice to refrain from using the subcutaneous route in patients with pendulous fat thighs. The patients receiving protein hydrolysate subcutaneously are those on parenteral feeding either before or after surgery. Another group

TABLE II.—BLOOD AMINO ACID LEVELS AFTER SUBCUTANEOUS INFUSION OF 500 C.C. OF PROTEIN HYDROLYSATE IN ONE AND ONE-HALF HOURS

Case	1	2	3	4	5	6	7	8	9	10	Average values	Per cent of normal
Normal level 100 c.c./mgm.	6.1	6.3	6.8	6.4	6.6	5.5	5.8	6.2	6.0	6.0	6.17	
After 250 c.c.	6.6	6.6	6.9	6.6	6.7	5.8	6.1	6.6	6.2	6.6	6.47	4.9
After 500 c.c.	7.2	6.9	7.2	7.3	6.9	6.5	6.5	6.8	6.6	7.2	6.91	13.0
After ½ hour	7.4	7.0	7.3	7.2	7.3	6.6	6.5	7.2	6.7	7.4	7.06	15.5
After 1 hour	7.4	6.9	7.3	7.0	7.3	6.5	6.4	7.0	6.6	7.3	6.97	13.0
After 1½ hours	7.0	6.8	7.0	6.6	7.2	6.0	6.2	6.8	6.3	7.2	6.71	10.0
After 2 hours	6.8	6.4	6.9	6.5	6.9	5.9	6.0	6.4	6.2	6.6	6.46	5.6

of patients who frequently are given this solution subcutaneously are infants or children, but these are not included in this report. We usually give only 1000 cubic centimeters a day to adults by the subcutaneous route. However, on occasions it becomes necessary to administer larger amounts to those patients who have a limited number of accessible veins or to those with cardiac diseases in whom the possibility of cardiac overloading is imminent. The largest single amount administered subcutaneously was 23,000 cubic centimeters over a 14 day period. In one instance a patient was kept in positive nitrogen balance for 8 days with parenteral protein hydrolysate subcutaneously as the sole source of proteins. She received 2000 or 3000 cubic centimeters daily by this route without any severe local reactions. After the fourth day, the thighs were tender and painful but we continued the therapy by the same route for 4 subsequent days.

Blood amino acid levels and urine chemical changes with subcutaneous injection of 500 c.c. of protein hydrolysate in one and one-half hours. Ten uncomplicated postoperative inguinal hernia patients were selected for these tolerance studies. These patients had been operated upon either 6 or 7 days previously, were on regular hospital diets, and ambulating. The 500 cubic centimeter infusion was administered into each thigh on the anteromedial aspect by gravity at a rate of 5 to 6 cubic centimeters per minute. At this speed there was no overdistention of the tissues or excessive bulging in the injected area. One per cent novocain was not used in these cases. Blood samples were drawn from either arm before the injection, after the infusion of 250 cubic centimeters, after 500 cubic centimeters and 30 minutes, 1 hour, 1½, and 2 hours following the completion of the infusion. A total 24 hour urine was collected fractionally the day of the infusion. Table II describes the changes in the blood amino acids.

The average amino acid level in these 10 patients was 6.17 milligrams per 100 cubic centimeters of serum and the individual findings varied between 5.5 milligrams and 6.8 milligrams per 100 cubic centimeters. After the infusion of 250 cubic centimeters, a 4.9 per cent elevation was noted, or an average rise of 0.3 milligram per 100 cubic centimeters of serum. The injection of the next 250 cubic centimeters produces an 8.1 per cent rise from the previous figure, or a 13 per cent increase above the original base level. There is a continued rise of the amino acids by 0.1 milligram in the 30 minute period following the completion of the injection. During the oncoming 30 minute period a slow decrease occurs in the blood amino acids. The findings in sequence are: 0.1 milligram, 1.5 per cent of normal; 0.2 milligram, 3.0 per cent of normal; and 0.3 milligram, 4.9 per cent of normal—a total decrease at this point (2 hours after completion of the infusion) of 0.6 milligram which represents 9.4 per cent of the normal level. However, the readings at this time still elicit a 5.1 per cent elevation of normal. From the previous rate of removal, we may infer a decrease to normal within another hour. Comparison of the rapid decrease in blood amino acids after intravenous infusion and the gradual slow decrease found with subcutaneous projects the idea of a gradual absorption of protein solu-

TABLE III.—AVERAGE BLOOD AMINO ACID LEVELS, DIFFERENCES, AND PER CENT OF NORMAL CHANGE FOR TEN CASES RECEIVING 500 C.C. OF PROTEIN HYDROLYSATE SUBCUTANEOUSLY IN ONE AND ONE-HALF HOURS

	Amino acid	Difference	Per cent of normal change —above normal—%	Differences in per cent of normal change—%
Normal level 100 c.c./mgm.	6.1			
After 250 c.c.	6.4	+0.3	4.9	+4.9
After 500 c.c.	6.9	+0.5	13.0	+8.1
After ½ hour	7.0	+0.1	14.5	+1.5
After 1 hour	6.9	—0.1	13.0	—1.5
After 1½ hours	6.7	—0.2	10.0	—3.0
After 2 hours	6.4	—0.3	5.1	—4.9

tions over a long period from the subcutaneous tissues after injection. These findings also imply that 4 to 6 hours are required for the infusion and absorption of 500 cubic centimeters of protein hydrolysate by this route.

Further interpretation with analysis of the amino acid levels obtained by subcutaneous infusions of a 5 per cent solution of protein hydrolysate of bovine blood is given in Table III.

The urinary findings in the administration here described are not revealing, for there was not any significant increase in the total nitrogen excretion for the 24 hour period and also amino acids were not detectable in the urine specimen (Table IV).

Leg measurements and rate of absorption as determined with phenolsulfonphthalein excretion as an indicator after the subcutaneous infusion of 1000 c.c. protein hydrolysate in two and one-half hours. A group of 5 uncomplicated ambulatory surgical patients was used for this investigation. Urine analysis of each patient before the test did not reveal any abnormal findings and blood urea nitrogen and nonprotein nitrogen values were within normal range.

Each patient was given a control test of phenolsulfonphthalein the day before the injection of the 1000 cubic centimeters of hydrolysate solution with a similar quantity of the dye. This gave figures of excretion for each patient. These were then compared to excretion values obtained when the dye was administered with the hydrolysate solution subcutaneously; therefore, an estimate of absorption. The validity of repeating the same type of dye test under somewhat similar circumstances is implied by the knowledge that kidney function can be measured rather closely because there is a close correlation between different readings of the same test done on successive days.

The following is the description of the control test: The patients voided and the specimen was discarded; 1 cubic centimeter of phenolsulfonphthalein was injected subcutaneously into the anteromedial surface of the thigh; the patient drank 1000 cubic centimeters of water; urine specimens were collected at 1 hour and 10 minutes, 2 hours and 10 minutes, and 3 hours and 10 minutes following the injection of the dye; the specimens were prepared as is outlined in the literature and compared to known standards for computation of the percentage of excretion (5).

TABLE IV.—CHEMICAL URINARY VALUES AFTER SUBCUTANEOUS INFUSION OF 500 C.C. PROTEIN HYDROLYSATE IN ONE AND ONE-HALF HOURS

Case	1	2	3	4	5	6	7	8	9	10	Average values
Urine nitrogen per 24 hours	10.2	10.7	11.5	10.4	10.7	10.3	10.1	10.3	11.4	9.2	10.48
Creatinine per 24 hours	1.3	1.18	1.05	1.15	1.25	1.2	1.3	1.1	1.2	1.2	1.17
Amino acid per 24 hours	0	0	0	0	0	0	0	0	0	0	0

TABLE V.—AVERAGE LEG MEASUREMENTS AND EXCRETION OF PHENOLSULFONPHTHALEIN AFTER SUBCUTANEOUS INJECTION OF 1000 C.C. OF PROTEIN HYDROLYSATE IN TWO AND ONE-HALF HOURS IN FIVE CASES

Time	75 min.	83 min.	After 1 hour	After 2 hours	After 3 hours	After 4 hours	Total excretion
Amount injected	500 c.c.	1000 c.c.					
Control 1 c.c. PSP per cent excretion			49	25	5.6		79.6
1000 c.c. P.H. and 1 c.c. PSP subcutaneously per cent excretion of PSP	8	12	19	16	9	9	73
Per cent excretion of control	9.4	23.9	46.5	68.5	81	89.7	89.7
Leg measurements Right	+0.75"	+1.5"	+1.25"	+0.55"	+0.19"	0	
Left	+0.75"	+1.5"	+1.0"	+0.5"	0	0	

The following day the absorption test, with 1000 cubic centimeters of protein hydrolysate subcutaneously, to which is added 0.6 gram of phenolsulfonphthalein, is conducted on the same patient. The details of the test are: The patient voids and the urine specimen is discarded; 1000 cubic centimeters of protein solution containing the dye is injected into the anteromedial surface by gravity into the subcutaneous tissues in an average time of 158 minutes or about 2½ hours at an infusion rate of approximately 6.25 cubic centimeters per minute; urine specimens were collected after the injection of 500 cubic centimeters after 1000 cubic centimeters, and 1, 2, 3, and 4 hours following the completion of the infusion; the percentage of dye excreted for each period was calculated by colorimetric comparison; leg measurements were obtained on each thigh during and after the infusion at regular intervals until the visual distention had disappeared; lastly, the percentage excretion of dye found with each period after the subcutaneous infusion of the hydrolysate and dye was calculated in terms of percentage of the total amount excreted by the control test performed the day before. Phenolsulfonphthalein dye has been used as an indicator for absorption (1). The results are depicted in Table V.

An average of 49 per cent of the dye was recovered in the urine 1 hour and 10 minutes after the injection of 1 cubic centimeter of phenolsulfonphthalein. The individual findings varied between 40 and 60 per cent. This represents the largest amount of dye excreted during the 3 hour period following the injection. The 5 cases revealed an average total excretion of 79.6 per cent and 85 per cent was the greatest amount per case.

The urinary excretion of phenolsulfonphthalein when injected slowly with 1000 cubic centimeters of protein hydrolysate is distinctly different from that seen in the control. One hour after completing the injection, a 39 per cent dye excretion is seen, whereas 49 per cent was recovered in the control test at this point. The average figures of excretion for the period during and 1 hour after the injection are 8 per cent after 500 cubic centimeters is infused, 12 per cent following the next 500 cubic centimeters infusion and 19 per cent in the first post infusion hour. Two hours after completing the infusion, 16 per cent of the dye is recovered, 9 per cent in the 3 hour period and 9 per cent in the last or 4 hour interval. Hence, a total excretion of 73 per cent of dye injected is noted in a 6½ hour period—6.6 per cent less than the amount recovered in a 3 hour period after injection of 1 cubic centimeter of dye subcutaneously.

The excretion figures obtained with the injection of dye dissolved in 1000 cubic centimeters of protein hydrolysate infer a rather steady and even absorption but with a maximum period at the end of 500 cubic centimeters and 1 hour after the injection of 1000 cubic centimeters. An 89 per cent excretion of the control is found in the 6½ hour period. Further, 72 per cent of the total excretion during the 6½ hour period occurs in the 4 hour period following the infusion.

The leg measurements closely correlate the blood amino acid levels previously described and the aforementioned excretion studies for the subcutaneous infusion of protein hydrolysate. The maximum increase in girth is noted at the end of the infusion (+1.5 inches in each leg). The enlargement subsides to normal within 3 hours after the injection.

A maximum blood amino acid level at the end of the subcutaneous administration and for 1 hour thereafter, and the maximum excretion of dye at the same periods, indicate maximum absorption during this period. The gradual decline in the blood amino acids, the excretion of dye and the leg size during the next 3 to 4 hours verify previous impressions of a slow, rather steady absorption for fluid given subcutaneously. Since the absorption time of subcutaneous infusion is time consuming in adults, it is likely that subcutaneous infusions should not be given more frequently than every 8 to 12 hours.

INTRAMUSCULAR ADMINISTRATION

The intramuscular route has been used chiefly for the injection of small amounts (1 c.c. to 10 c.c.) of solutions and drugs in adults. Muscle tissues are vascular and contain a large supply of lymphatics; hence, absorption should be rapid and adequate. One of the early reports on the use of intramuscular route was that of Nassau in 1926 who described encouraging results. Later descriptions appeared in Germany (Stamm). Glaser recommended the lateral and anterolateral surfaces of the thigh.

Our interest in intramuscular infusions of large quantities of protein hydrolysate stemmed from the experience of the author with plasma intramuscularly and the discomfort associated with lengthy subcutaneous infusion. Patients on parenteral therapy alone require 3000 to 4000 or more cubic centimeters per day. In view of the hospital management of surgical patients, the usual method of administering 3000 cubic centimeters of fluid per day is to give 1000 cubic centimeters intravenously in the morning, 1000 cubic centimeters subcutaneously in the afternoon, and 1000 cubic centimeters intravenously in the evening. By this plan, the patient is immobilized for at least 6 to 8 hours of the waking period, if all of the infusions are administered with ease (1½ hours for intravenous, and 2½ to 4 hours for subcutaneous). Thus the patient is able to move about for only 5 hours of his hospital day. If the infusions require longer periods, such as 3 to 4 hours for intravenous, one can readily see that the patient is on his back all day if he is to receive adequate fluid and nutrition.

Technique. One thousand cubic centimeters of protein hydrolysate can be infused into the vastus lateralis of each leg simultaneously within 30 minutes without undue discomfort. The site selected for the infusion is the lateral at a point midway between the anterior and posterior surfaces and at the junction of the upper and middle thirds. A 2½ inch No. 15 to 18 gauge needle is used with the bottle suspended 3 feet from the level of the thigh, a Y connection is used so that both thighs are injected at the same time. One per cent or 2 per cent novocain to the amount of 50 cubic centimeters is usually added to each bottle for local novocainization. It is best to have the legs flexed at the knee so as partially to relax the iliotibial band. The needle is thrust sharply at a 45 degree angle to the long axis of the thigh with the point directed upward or cephalad. After the fascia lata is pierced, the needle is inserted into the substance of the muscle at a 15 degree angle to the side of the thigh. There is a sense of give when the needle pierces the fascia. It is important to keep the end of the needle away from the bone; the needle should not be submerged beyond the middle of the transverse diameter of the vastus lateralis at the point of injection. No taping of the needles to the skin is necessary as the fascia lata will tend to fix the needle. The stopcock in the set is opened wide and the fluid is allowed to pour in. The first 200 to 300 cubic centimeters are administered in a matter of 3 to 4 minutes. Not infrequently the patient complains of a sense of fullness in the legs and describes a smarting sensation which disappears after the infusion of about 300 cubic centimeters. The flow is then slightly decreased but still continues at a very rapid rate. As the last 200 to 300 cubic centimeters are approached, the flow decreases still more but

TABLE VI.—BLOOD AMINO ACID LEVELS AND UREA NITROGEN AFTER RAPID INTRAMUSCULAR INJECTION OF 1000 C.C. PROTEIN HYDROLYSATE IN THIRTY MINUTES IN BOTH THIGHS

Case	1	2	3	4	5	6	7	8	9	10	Average amino acid	Average blood urea
Normal level 100 c.c./mgm.	6.0	6.4	5.8	6.1	6.3	6.0	5.9	6.5	6.4	6.6	6.2	12.4
After 1000 c.c. P.H. intramus. in 30 min.	7.4	7.3	6.9	7.2	7.5	7.0	6.8	7.8	7.2	7.5	7.26	12.8
After 1 hour	7.6	7.5	7.2	7.2	7.6	7.3	7.3	7.8	7.3	7.7	7.4	12.6
After 2 hours	7.4	7.2	6.8	6.7	7.2	7.2	7.0	7.0	7.0	7.3	7.0	12.8
After 3 hours	6.4	6.7	5.9	6.3	7.0	6.4	6.5	6.7	6.6	6.6	6.5	11.8
After 24 hours	6.1	6.5	5.7	5.9	6.4	6.1	6.2	6.4	6.5	6.5	6.2	12.3

is not slow enough to count the drops accurately in the "vaco drip." There is a bulging in the lateral compartment of the thigh. There is no pain after the early part of the infusion but patients complain of a heaviness in the leg following the injection, and this is frequently described as a "dead leg." This sensation disappears with absorption. Few patients have any difficulty with ambulation after the total infusion. In the early part of our experience with intramuscular infusions, we gave 1000 cubic centimeters into each limb, but this produced excessive distention and tension. This distention was occasionally severe enough to produce the leakage of fluid from the puncture site. Needles in which holes were bored in the sides were also tried. These needles permitted a faster flow than is seen with the standard needles.

One hundred and seventy intramuscular infusions of 1000 cubic centimeters of protein hydrolysate have been administered to 78 patients without recognizable local reactions, irritations, or failure of absorption.

Blood amino acid levels, urea nitrogen, and urine chemical changes after rapid intramuscular injection of 1000 c.c. protein hydrolysate in thirty minutes. This study was performed with 10 uncomplicated postoperative surgical patients. The liter of hydrolysate was administered in 30 minutes by the previously described technique. Blood samples were drawn before the infusion, after the 1000 cubic centimeter injection, 1 hour, 2 hours, 3 hours, and at the end of the 24 hour period following the administration. Fractional samples of urine were collected throughout the 24 hour period.

The individual amino acid levels, the average amino acid levels, and the average blood urea nitrogen for the 10 individuals studied are presented in Table VI. As will be noted, the maximum rise occurs at the end of the infusion and in the first hour following the end of the injection. A 15.4 per cent or +1.0 milligram per 100 cubic centimeters of serum rise is seen with the end of the injection. A maximum response of 1.4 milligrams developed in 1 case and the least effect was represented by a 0.9 milligram elevation for this period. One hour following the injection, the average rise was 0.2 milligram above the previous level with total rise above normal of 19.3 per cent. Further analyses of the blood levels found at 1 hour after end of the infusion indicate no rise in 3 instances. During the next 2 hour period a decrease of 17.8 per cent is seen—in order the figures are 13 per cent and 4.8 per cent decreases. The amino acid blood levels are normal at the end of the 24 hour period. These figures indicate maximum absorption with the completion of the infusion and an almost equal absorption rate within the first hour following the injection. The rather precipitous decline in the second postinfusion hour shows that the greater percentage of the injected protein hydrolysate is absorbed within a 2 or 2½ hour period following the injection.

The average blood urea levels performed at the same intervals as the blood amino acids are not significant. Further, the total nitrogen output for the 24 hours of study varied between 11.1 and 13.1 grams, and averaged 12.4 grams.

A composite presentation of the above findings is illustrated in Table VII.

TABLE VII.—AVERAGE BLOOD AMINO ACID LEVELS, DIFFERENCES, PERCENTAGE OF NORMAL CHANGE AND AVERAGE BLOOD UREA NITROGEN FOR TEN CASES AFTER RAPID INTRAMUSCULAR INJECTION OF 1000 C.C. PROTEIN HYDROLYSATE IN THIRTY MINUTES IN BOTH THIGHS

	Amino acid	Difference	Per cent of normal change —above normal	Differences in per cent of normal change	Urea nitrogen
Normal level 100 c.c./mgm.	6.2				12.4
After 1000 c.c. P.H. intramuscularly	7.26	+1.0	15.4	+15.4	12.8
After 1 hour	7.4	+1.2	19.3	+ 3.9	12.6
After 2 hours	7.0	+0.8	13.0	— 6.3	12.8
After 3 hours	6.5	+0.3	4.8	— 8.2	11.8
After 24 hours	6.2	0		0	12.3

Average blood amino acid levels, leg measurements and rate of absorption as determined with phenolsulfonphthalein excretion as an indicator after the rapid intramuscular injection of 1000 c.c. of protein hydrolysate in about thirty minutes in 5 cases. The method of injection is as described. The procedure for investigation is similar to that related under subcutaneous infusions except for the following details: (1) control injection of dye (1 c.c.) was made into the vastus lateralis of the leg; (2) blood samples were drawn at the same intervals as the collection of urine samples.

The injection rate in this experimental study and in the other infusions performed for clinical indications is about 36 cubic centimeters per minute.

Table VIII demonstrates the findings.

The amount of dye excreted in the control test closely resembles the findings previously described in the subcutaneous group, viz.; 79.6 per cent in 3 hours in subcutaneous and 69.4 per cent in 3 hours in the intramuscular series.

After the intramuscular injection of the hydrolysate solution with 0.6 gram of phenolsulfonphthalein, 32 per cent of dye is excreted 1 hour after the total infusion, 22 per cent at the end of the next hour, 11 per cent following the third hour and 2.2 per cent after 4 hours. In percentage excretion of normal, the above figures represent in the same sequence, a 46 per cent, 77 per cent, 93 per cent, and 96 per cent excretion of normal.

Five hundred cubic centimeters of fluid or approximately 250 cubic centimeters in each leg causes an increase in size of 1.3 inches and with the total injection the thighs are increased to about 2.6 to 2.75 inches above normal. The thighs begin to decrease soon after the end of the infusion by about 1 inch an hour, so that they have returned to normal size within 3 hours after the completion of the liquid infusion. Therefore, 1000 cubic centimeters of

TABLE VIII.—AVERAGE BLOOD AMINO ACID LEVELS, LEG MEASUREMENTS, AND EXCRETION OF PHENOLSULFONPHTHALEIN AFTER RAPID INTRAMUSCULAR INJECTION OF 1000 C.C. PROTEIN HYDROLYSATE IN FIVE CASES

Time	9 min.	17.8 min.	After 1 hour	After 2 hours	After 3 hours	After 4 hours	Total
Amount injected	500 c.c.	1000 c.c.					
Blood amino acid, mgm.		7.26	7.4	7.0	6.5	6.2 (24 hours)	
Control 1 c.c. PSP per cent excretion			41	22	6.4		69.4
1000 c.c. P.H. and 1 c.c. PSP intramuscularly per cent excretion of PSP			32	22	11	2.2	67.2
Per cent excretion of control			46	77	93	96	96
Leg measurements Right	+1.3″	+2.75″	+1.9″	+1.0″	0		
Left	+1.3′	+2.6″	+1.9″	+0.7″	0		

fluid injected rapidly into the vastus lateralis is absorbed within a 2 or 2½ hour period. Hence, one can administer intramuscular infusions of similar quantity every 4 to 6 hours.

A male patient with peritonitis from a perforated duodenal ulcer was given daily injections of 1000 cubic centimeters of protein hydrolysate solution in each thigh rapidly (30 minutes) for 7 successive days as part of his fluid therapy. A biopsy of the vastus lateralis was taken the day following the last injection. Gross examination of the muscle did not reveal any changes in color, striations, or configurations. Microscopic sections showed normal muscle bundles. There was no separation of the muscle fibers, fibrosis, fragmentation, or cellular infiltration as evidence of inflammation or irritation.

ADVANTAGES AND DISADVANTAGES OF EACH ROUTE

In view of this report, it seems evident, that parenteral protein hydrolysate prepared by enzymatic digestion of bovine blood is a safe solution in surgical patients when given intravenously, subcutaneously, and rapidly intramuscularly. These findings verify an earlier report (12).

Intravenous administration of fluids is by far the most commonly used route. Though it has the advantages of direct introduction of medication and of ease of administration of large amounts at one time or continuously, it has numerous disadvantages. An intravenous infusion is only as effective as the flow through the needle; and the flow through the needle is directly related to the correct introduction of the needle into the vein. The ease or difficulty encountered with venipuncture is dependent on: "(1) accessibility of the veins (collapsed or masked by subcutaneous fat); (2) size of the veins; (3) thickness of the wall of the veins; (4) degree of fixation of the vein; (5) size of the needle in relation to the size of the vein; (6) sharpness of the needle; (7) the degree of bevel of the needle; (8) cleanliness of the needle; (9) experience of the individual doing the injection; (10) position of the needle in the vein (complete, incomplete, angulation, etc.); (11) age of the patient; (12) co-operation of the patient" (White, 13).

Though intravenous medications have been refined to reduce reaction incidences, the danger of reactions is still an imminent one. Most reactions depend on factors within the patient, those in the equipment, and those due to the solution. The reactions which may result from faulty equipment are due to pyrogens, contaminants, rubber tubing, or alkalies. Too rapid infusions of solutions may cause overloading, pulmonary edema, or systemic reactions such as vomiting, flushing, etc. These studies indicate that the tolerance of protein hydrolysate is great. As much as 25 to 30 cubic centimeters may be injected per minute in 1000 cubic centimeter doses without fear of frequent systemic reactions. Vomiting and nausea are seen only if 50 to 150 cubic centimeters per minute is injected in quantities of 700 to 1800 cubic centimeters. A recent report by Smyth and associates indicates that "the incidence of nausea with hydrolysates depends on the amino acid composition rather than on the average rate of administration or on the plasma amino acid nitrogen level." This author also indicates that there may be a close relationship between glutamic and aspartic acid contents with nausea and vomiting after intravenous injection. The solution studied and presented herein contains 10.34 per cent glutamic acid and 4.26 per cent aspartic acid.

After the injection of 50 grams of protein hydrolysate intravenously at 17 cubic centimeters per minute, there is an average rise of 2.6 milligrams of amino acids per 100 cubic centimeters of serum or a 42.2 per cent elevation above normal. Two hours later the major part of the circulating amino acids is removed. A point of interest is the slight decrease during the first postinfusion hour and the maximum removal in the next hour. Hoffman, Kozoll, and Osgood report the following findings with "parenamine." Injection of 45 grams of parenamine intravenously at slow speeds produced an average plasma amino acid rise of +4.9 milligrams per 100 cubic centimeters during the injection with a return to normal in 2 hours. The difference in our amino acid levels and those reported by Hoffman and associates may be partially due to the difference in amino acid content of the two preparations. The preparation of protein

hydrolysate used in this study contains 50 to 55 per cent alpha amino nitrogen whereas parenamine contains 70 per cent.

Other disadvantages of intravenous protein hydrolysate are the possibility of thrombosis and phlebitis with prolonged infusions. Likewise, administration of large amounts of hydrolysate solution produces a rise in blood urea nitrogen and an increase output of nitrogen in the urine as urea and amino acids.

Subcutaneous infusions are simply performed by the average person. However, administration is time consuming (2 to 6 hours for 1000 c.c.), painful, requires immobilization of the patient for long periods, and if given in excessive quantities can cause tissue irritation.

Our review reveals that this route is a safe one if 1000 cubic centimeters is administered daily. When 1000 cubic centimeters is given at a rate of 6.25 cubic centimeters per minute there is a slow even absorption throughout the 2½ hour period of infusion and the following 4 hours. The percentage absorbed is 9.4 of the total in the first 75 minutes of administration, 14.5 per cent in the following 83 minutes, 22.6 per cent in the first hour after infusion, 22.0 per cent the second hour after the infusion, 12.5 per cent the third hour, after infusion and 8 per cent in the fourth hour. Therefore, a total absorption of 89.7 per cent of the total injection when compared to the control figures obtained with phenolsulfonphthalein excretion. These absorption figures are based on the excretion of dye absorbed with hydrolysate. It may be said that 6½ hours or more are required for the successful infusion and absorption of 1000 cubic centimeters of protein hydrolysate. The leg measurements roughly correspond to the excretion studies. No systemic reactions are seen with hydrolysate given subcutaneously because the absorption is too slow to raise the level of amino acids to anywhere near the toxic level of 14 milligrams per cent.

Rapid intramuscular infusions are safe, easy to administer, produce no demonstrable abnormal reactions of the tissues, and do not immobilize the patient for long periods. Both blood amino acid levels and absorption studies show a constant rather rapid absorption within 3 hours after the infusion. In the first 2 postinfusion hours, 77 per cent of the total is absorbed. The figures for each hour period are 46 per cent in the first hour after infusion, 31 per cent in the next hour, 16 per cent the third hour, and 3 per cent in the fourth hour. When these figures are compared with the subcutaneous absorption findings, one notes a similar total absorption at the period of 1 hour after the infusion. But 3½ hours was required for the same results by the subcutaneous route, whereas only 1½ by the intramuscular. Further, 9 per cent more is absorbed in the second postinfusion period with intramuscular and 12 per cent more in the third hour period when compared to the subcutaneous route. Hence, 3½ to 4 hours is required for the administration and absorption of 1000 cubic centimeters of protein hydrolysate intramuscularly with only 30 minutes for the injection, whereas 6½ hours are required for subcutaneous infusions, in which 2½ hours are needed for the injection. The reaction and discomfort are much less by the intramuscular route. Finley, Shaffer, and Altenberg described the parenteral administration of fluid beneath the fascia lata in 1944. These authors found that 56 minutes was the average time for delivery of 1000 cubic centimeters of saline or 5 per cent dextrose in 261 consecutive subfascial infusions. These authors also noted that 3½ hours was required for absorption after the complete delivery of the solution. Their figures correspond closely with ours.

CONCLUSIONS

1. A 5 per cent parenteral protein hydrolysate in distilled water which is prepared from bovine blood by enzymatic digestion has been administered to a large group of surgical patients intravenously, subcutaneously, and rapidly intramuscularly with a conspicuously low reaction rate.

2. The end product contains 0.275 gram per 100 cubic centimeters of alpha amino nitrogen which represents about 50 per cent of the total nitrogen; approximately 0.30 per 100 cubic centimeters of sodium chloride, and a *p*H of 6.20 to 6.40.

3. In 2003 consecutive intravenous infusions of 1000 cubic centimeters each, in 320

preoperative and postoperative surgical patients there were 0.72 per cent reactions: 0.14 per cent were systemic, 0.49 per cent were pyrogenic, and 0.09 per cent were allergic. The systemic reactions were seen only with the first batch of material investigated in the early part of the investigation. The average rate of infusion varied between 12 and 17 cubic centimeters per minute, a speed commensurate with practical administration of fluids.

4. No acute ascending thrombophlebitis or ascending thrombosis was found in any case receiving 1000 cubic centimeter infusions in 1 or 1½ hours even though repeated infusions were given on subsequent days in either antecubital veins. A procedure for decreasing the local thrombosis and the disadvantages of prolonged infusions are presented.

5. The blood amino acids rise 2.6 milligrams per 100 cubic centimeters or 42.2 per cent above normal after the infusion of 1000 cubic centimeters of protein hydrolysate in 1 hour. Two hours is required for the removal of excess amino acids accumulating in the blood after the injection. No increase in urinary nitrogen or amino acids is found in the urine with the intravenous administration of 1 liter of hydrolysate solution.

6. Four hundred and twenty subcutaneous infusions of 1000 cubic centimeters were given at a rate of 6.25 cubic centimeters per minute in 126 patients without failure of absorption or local difficulties.

7. Subcutaneous infusions of 500 cubic centimeters of protein hydrolysate in both thighs and in 1½ hours cause a 13 per cent rise in blood amino acids with an average maximum rise to 6.91 grams per 1000 cubic centimeters. This rise continues in the next 30 minutes but then decreases and has returned to normal 2 hours after the end of the injection. Absorption studies as indicated by the excretion of absorbed phenolsulfonphthalein indicate that 6½ hours are required for the introduction and absorption of 1000 cubic centimeters of protein hydrolysate. Hence, only 1000 cubic centimeters of fluid can be given every 8 to 12 hours by the subcutaneous route.

8. A method of estimating absorption of fluids from subcutaneous and intramuscular tissues with the excretion of absorbed phenolsulfonphthalein is presented.

9. One hundred and seventy intramuscular injections of 1000 cubic centimeters of protein hydrolysate in 78 patients at a rate of 33 cubic centimeters per minute show rapid absorption in 3 hours, no irritations or local reactions, no failure of absorption and a negligible amount of pain or discomfort.

10. Blood amino acid levels, after the intramuscular injection of 1000 cubic centimeters in 30 minutes, indicate a maximal rise at the end of the infusion and a decrease to near normal within 3 hours after the injection. Absorption studies reveal similar findings in which 93 per cent is absorbed in 3 hours after the rapid infusion of 1000 cubic centimeters into the vastus lateralis.

11. Pathologic slides do not show any abnormal tissue reaction in a patient who received into the same leg 1000 cubic centimeters on 7 consecutive days.

12. A comparison of intravenous, subcutaneous, intramuscular infusions is made, and the advantages and disadvantages of each route are discussed.

13. Bovine protein hydrolysate is a safe parenteral fluid for patients who require proteins by intravenous, subcutaneous, and intramuscular routes.

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CONGENITAL OBSTRUCTION OF THE BILE DUCTS

IN recent years, a greater interest in surgical conditions of infancy and childhood has resulted in the increasing number of congenital anomalies that are reported. With increasing experience, successful results are being obtained in the surgical treatment of these conditions, many of which, 30 years ago, were uniformly fatal. Developmental anomalies causing obstruction in the extrahepatic bile ducts are examples of these conditions. Jaundice in the newborn is a very common finding, and the case of jaundice that is the result of a congenital obstructive lesion in the extrahepatic ducts must be recognized in treating icterus in early life. This diagnosis may be difficult to establish in the first two to three weeks of life. Fortunately, as far as prognosis goes, it is not essential that diagnosis be established this early. The prognosis seems equally favorable, in those cases that are amenable to surgical treatment, even though the diagnosis is not established for several weeks. It is desirable, however, that these infants be operated on before the fourth or fifth week of life. While the treatment in these cases is surgical, there is always ample time to be sure of the diagnosis.

The diagnosis is made largely by the exclusion of other causes of jaundice in early life. The differential points are usually easily determined. The following causes must be considered and excluded: Icterus neonatorum, or physiologic jaundice, is generally not serious and usually disappears between the second and third week of life. While the degree of icterus present in physiologic jaundice may at first be the same as that in obstructive jaundice, it does not progress. There is seldom an enlarged liver and the jaundice soon starts to subside. The stools contain bile and there is seldom bile in any large amount in the urine.

Icterus due to erythroblastosis fetalis comes on early and examination of the blood smear may show an increased number of erythrocytes. The spleen is enlarged rather early in this disease which is not the case in congenital obstruction of the bile ducts. Appropriate laboratory tests of the child's and the mother's blood will promptly confirm or exclude the presence of Rh incompatibility and any abnormal antibodies. In erythroblastosis fetalis, unless suitable treatment by appropriate transfusion is instituted there may be an early fatal outcome. However, it is well to remember that in the recovery stage of erythroblastosis fetalis with jaundice there may be an obstructive phase due to severe liver damage. If the suitable laboratory tests of the child and mother, as referred to above, have not been done they should be performed at this stage to rule out this possibility as a cause of the icterus.

Icterus in the newborn caused by hemolysis, whether from sepsis or from hemolytic crises, is not accompanied by the acholic stools characteristic of congenital obstruction of the bile ducts, nor is there a significant amount of bile in the urine. The icteric index is not increased and the symptoms are not, as a rule, progressive. In familial hemolytic icterus there is a striking increased fragility of the red blood cells, which is the important laboratory finding.

Syphilis, as a cause of jaundice, will be shown by appropriate examination of the patient's and parents' blood and usually the x-ray examination will give confirmatory evidence of syphilis in the patient's bones.

In congenital obstruction of the bile ducts, the jaundice is prompt in appearance, often being present at birth or very shortly thereafter. Characteristically, it becomes slowly but progressively more intense as the days and weeks pass and it has a rather peculiar greenish-yellow color rather than the bright yellow tinge seen in other types at this age. The stools are clay-colored or white, show no bile from the start, and continue to be acholic. Very occasionally, a positive test for bile may be obtained or the stool may show gross evidence of bile on the surface. Such findings have been observed in our series where operation has proved that there was atresia or even complete absence of the extrahepatic ducts. To explain this finding, it is presumed that a certain amount of bile may be excreted into the gastrointestinal tract from the intestinal mucosa, the bile being carried there by the blood stream.

Cases of congenital atresia show no evidence of sepsis as a cause for the jaundice unless there be a concomitant infection. The icteric index is elevated. In our series these ranged from 50 to 325, the average being 150. The fragility of the red cells is normal, or even decreased. The urine is dark colored and will persistently give a positive test for bile pigment.

In other words, the diagnosis is arrived at with considerable certainty by excluding other causes of jaundice. In doubtful cases nothing is lost by waiting a sufficient period of time to exclude these causes. The general condition of these patients remains surprisingly good even after two to three months. It is, however, desirable to operate as soon as the diagnosis is established, which is usually possible by the fourth week. Unless the condition is very advanced, abdominal findings are confined to an enlarged liver, the edge of which may extend well down below the costal margin. It is sometimes possible to feel the roughening, characteristic of biliary cirrhosis. Ordinarily, the spleen is only slightly enlarged, if at all. In advanced cases ascitic fluid may be present. The state of nutrition is usually surprisingly good, though the older infants may give some history of fat intolerance when on the ordinary formula for their age. Blood studies rarely show anything other than a secondary anemia. Surprisingly enough, the clotting time is seldom increased, particularly in infants under two to three months of age. The prothrombin values may be somewhat lowered though this is not always the case. The infant shows nothing like the profound toxemia that is usually present when the icterus is due to sepsis. The gross findings associated with these obstructions are a generalized, persistent and increasing icterus with a gradually increasing size of the liver.

The treatment is surgical. The extrahepatic biliary system should be very carefully inspected through an incision of adequate length, preferably a right rectus incision. The procedure takes time and must be done with great care and with particular attention to the control of hemorrhage. The gall bladder is sought for first and, if present, is followed down to the

area of the hepatic and common duct. If the gall bladder obviously contains bile, the prognosis for that individual becomes much more favorable. Oftentimes, the gall bladder is rudimentary and even when it has a lumen it may prove to contain only a clear, viscid fluid with no bile pigment, which indicates that there is no communication between this organ and the other extrabiliary ducts. Distention of the gall bladder with saline solution may give valuable information as to whether it communicates with the hepatic and common ducts. If these ducts communicate, but are very small, such distention permits of their easier identification. The gall bladder may be absent. A great variety of anomalies may be encountered. The essential finding, as far as the chance of successful surgery is concerned, is the presence of the hepatic duct. If nothing in this region can be found, the prognosis is hopeless. Even a very small hepatic duct can be successfully anastomosed to the duodenum, and this is usually best done over a small piece of soft rubber catheter which should be not more than two centimeters in length. A longer tube may not be passed with ease after healing has taken place. If the hepatic duct, a cystic duct, and a gall bladder are present and continuous, the operation of choice is to anastomose the gall bladder to the duodenum. This procedure is far better than anastomosing it to the stomach. If there is any appreciable length to the common duct, however, it is better to anastomose the common duct to the duodenum.

The usual careful attention to preoperative and postoperative care, particularly as regards fluid and electrolyte balance must be observed. In about one-fifth of the cases, the structural anomaly present will permit of some successful anastomosis between the extrahepatic ducts and the gastrointestinal tract. In the remaining and discouragingly large percentage of cases, however, no extrahepatic ducts are present. Many measures have been employed in such cases to create an artificial communication between the liver itself and the gastrointestinal tract. These efforts are usually futile, because postmortem examination of patients who have no extrahepatic ducts, does show, in a large percentage of cases, an associated intrahepatic developmental pathology of such a degree that there is, practically speaking, no biliary tree of sufficient size or development to premit any form of anastomosis between the liver and the gastrointestinal tract that will effectively drain bile.

The infants who have been successfully operated on, however, have shown a very satisfactory development. They have not shown evidence of liver damage for as long as 15 years after operation. This is surprising when one considers the apparently advanced state of cirrhosis present at the time of operation. It has been particularly interesting that they have not shown any notable tendency for a retrograde cholangitis, even though the stoma between the bile duct and the intestine has, in most cases, been relatively large, and presumably with a complete absence of any sphincter action. In infants who have had the gall bladder anastomosed to the gastrointestinal tract we have, as yet, no cases where stones have developed. It is too soon to state, and futile to predict, how many will form stones.

We believe that all infants with congenital atresia or stenosis of the bile ducts should be given the benefit of an exploratory operation. The diagnosis is relatively easy to establish and even though only 20 per cent or less will be found to have a condition that can be remedied by surgery, it is worthwhile to make the attempt. The prognosis, without operation, is uniformly fatal, though these patients may live for a surprising number of months.

THOMAS H. LANMAN.

CONGENITAL ANOMALIES OF THE BILE DUCTS AND ADJACENT BLOOD VESSELS

IN no region of the human body are anomalies so common as in the bile ducts and adjacent blood vessels. It is, therefore, impossible to present any pattern as the "normal"; a composite of specimens least abnormal becomes the substitute for normal anatomy in this area. It is likewise true that in no region of the human body do anomalies result in so many serious accidents or consequences following surgery. Although carelessness and haste are vital causes of accidents resulting in stricture or absence of the common duct, the majority of these accidents would probably not occur if there were not such a great variation in anatomy.

In 39 cases of stricture of the common duct observed at Illinois Research Hospital over a 10 year period, operative trauma was definitely identified as the cause of the stricture in 64 per cent. In an additional 20 per cent of cases jaundice developed 4 months to 5 years following cholecystectomy. Although inflammation of some type may be considered to be the cause of stenosis in this group, the fact remains that a gall-bladder operation (cholecystectomy in every instance) preceded stricture formation. Other surgeons report similar figures relative to operative trauma as the etiologic factor (Cattell, 80 per cent; Walters, 90 per cent). In 13 per cent of our series, chronic sclerosing pancreatitis was the cause of the stricture. In only one patient (3 per cent) was there no history of operation preceding the stricture; the cause of obstruction in this instance was an adhesion compressing the duct without actual fibrosis or damage to the duct wall. Causes of stricture not related to anomalies are ulceration of the duct by stone, chronic sclerosing pancreatitis, neglected cholangitis and abscess about the duct. Rarely indeed can choledochostomy be identified as the primary cause of stricture.

Extreme mobility of the common duct is a common cause of injury to this structure, particularly if the cystic duct is short and wide. In this case traction on the gall bladder will make the cystic and common duct appear as one continuous structure (namely cystic duct). If more than average care is not exercised by the surgeon, he may thereby identify the common duct as cystic, and ligate it, thus producing a complete obstruction of the common duct. On other occasions the cystic duct is long and lying against the common, as was noted in 20 to 25 per cent of cases by Eisendrath. Strenuous efforts to separate it from the common duct may result in so much damage to the latter structure that a stricture develops later. An accessory hepatic duct (noted by Flint in 15 per cent of cases) may give rise to stricture of the common duct by a mechanism not generally appreciated. If the accessory duct is cut unknowingly during cholecystectomy and not ligated, bile may accumulate around the common duct after operation and give rise to so much inflammation in the wall of the duct as to result in stricture formation at a later date. Section of an accessory hepatic duct is very apt to be unnoticed because flow of bile is commonly decreased to a marked degree during the operation, thereby depriving the surgeon of the best method of detecting its division. Although abscess formation about the common duct is no doubt an important cause of stricture, the author is convinced that accumulation of bile is probably a more common cause.

Arterial anomalies give rise to strictures of the common duct primarily because the duct is injured during the process of stopping hemorrhage from the injured anomalous vessel. In 15 per cent of cases (Flint), an accessory

cystic artery is present. After the surgeon has identified one cystic artery and ligated it, he is apt to proceed rapidly with the rest of the dissection, and during this haste cut the other cystic artery. Division of either cystic artery will give rise to hemorrhage immediately adjacent to the common duct. If the surgeon should lose his presence of mind, and begin to stab blindly in the bloody field for the bleeding artery instead of controlling the hemorrhage by insertion of his index finger in the foramen of Winslow with compression of the hepatic artery against his thumb, the common duct may be caught and ligated with the bleeding vessel. In 16 per cent of cases (Flint) the cystic artery is anterior to the common duct. The surgeon does not expect to find the artery in this location and during the process of incising the peritoneum and fibrous tissue over the common duct may cut the cystic artery. Control of the hemorrhage by improper means, as mentioned above, may likewise result in ligation of a portion of the common duct with the bleeding vessel. In 12 per cent of cases the right hepatic artery crosses to the right, anterior to the common duct (Flint). In about 20 per cent of cases it proceeds from its normal position under the common duct to the right and anteriorly so that it parallels the cystic duct. In either of the two positions just mentioned it may be injured during dissection. In either case hemorrhage will be brisk. If the hemorrhage is not controlled skilfully and the bleeding point ligated carefully the common duct may be damaged. However, in about 50 per cent of cases division and ligation of the right hepatic artery will result in death of the patient within a few days following operation. In these cases there will naturally be no opportunity for development of a stricture. In 20 per cent of cases the gastroduodenal artery lies anterior to the common duct (Eisendrath). Although this vessel usually lies too far inferior to the area of dissection to be damaged, it might easily be injured if the surgeon should carelessly attempt to isolate the distal portion of the common duct. Hemorrhage would be very brisk and its control might result in injury to the wall of the common duct. In about 50 per cent of cases there is a small branch of the right hepatic or gastroduodenal artery in the anterior wall of the common duct. Although this artery is usually severed when the duct is opened for extraction of stones, the resultant hemorrhage is rarely severe enough to result in significant damage to the duct during control of the bleeding joint.

About the only anomaly of the gall bladder giving rise to stricture of the common duct is an unusually large and pendulous Hartmann's pouch, which lies on the common duct. Since adhesions are common in this area, it is obvious that damage may be inflicted on the common duct unless separation of the pouch from the common duct is carried out with extreme care (R. Graham).

In about 90 per cent of cases the portal vein bifurcates before entering the liver, and in the remainder of cases enters the liver before bifurcation. Rarely is this anomaly related to injury or stricture of the common duct. The common hepatic duct bifurcates inside the liver in about 90 per cent of cases, and outside the liver in the remainder. This anomaly also is seldom related to injury to the duct itself, but when the hepatic ducts join outside the liver, and a structure is present at this site, the repair is greatly complicated by the anomalous bifurcation. WARREN H. COLE.

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WALT WHITMAN — A CASE HISTORY

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WALT WHITMAN, the "Good Gray Poet," the "poet of democracy," has been the center of many controversies since the publication of his *Leaves of Grass* in 1855. Although Walt was the prophet of the perfect body—"I sing the body electric"—the last 30 years of his life were dogged by ill health. He finally died 2 months before his 73rd birthday, a veritable pathological museum. Although there are many references to the state of Whitman's health, particularly during the later period of his life, these are largely superficial and subjective. Examination of the available records, however, has allowed us to reconstruct, at least in outline, the tremendous struggles waged by one of our literary giants against physical and mental deterioration.

Walt Whitman was born at West Hills, Long Island, on May 31, 1819, the second of 9 children. His father, Walter Whitman, was a farmer and carpenter. When Walt was 4 years old the family moved to Brooklyn, then a village of about seven thousand inhabitants. He was educated in the common schools of Brooklyn and at 13 left school and began work as an errand boy in a doctor's office. Before reaching 15 he became an apprentice typesetter in the printing office of the *Long Island Patriot;* at 18 he tried teaching for a time in Long Island country schools, but in 1839 he turned again to printing, now as publisher of his own newspaper, *The Long Islander*, in Huntington. After a year or two he gave up the paper and returned to Brooklyn, where in 1841 he became editor, briefly, of the *Daily Aurora*, at the same time writing essays, stories, and poems for other newspapers and magazines. In 1842, he wrote a temperance novel, *Franklin Evans*. All these productions, whether prose or verse, show very little of the distinctive manner that was to mark Walt's later writings; they show, in fact, very little merit of any kind.

With frequent vacations on rural Long Island, Whitman remained in Brooklyn and New York until early in 1848 when, having lost his post as editor of the Brooklyn *Eagle*, he set out for New Orleans to become editor of a newly established paper there. After a few months he returned to New York, where he continued to work as editor and writer and, for a time, as carpenter. In the spring of 1855, at the age of 36, at a Brooklyn printing house, he began to set type for a book of poems he had written, and in July the first edition of *Leaves of Grass* appeared.

This amazing publication, utterly different from almost all he had earlier published, met for the most part with indifference or contempt in the literary world. Praise came chiefly from Emerson, who wrote in a letter to Whitman: "I find it the most extraordinary piece of wit and wisdom that America has yet contributed. I greet you at the beginning of a great career. . . ." The most truly appreciative reviews were written by Whitman himself.[1]

Further editions of *Leaves of Grass* appeared in 1856 and in 1860, the latter from a Boston publishing house, which collapsed with the coming of the Civil War. Walt's brother George enlisted promptly when the war began, while Walt stayed quietly in Brooklyn, writing poetry and visiting sick and disabled stage drivers in the hospitals. In December of 1862, when word came that George had been wounded, Walt left for the front. He found George nearly recovered, but encountered many sick and helpless soldiers who needed his care; accordingly, he stayed in Washington to

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[1]He published anonymously several reviews, one of which began: "An American bard at last! One of the roughs, large, proud, affectionate, eating, drinking, and breeding, his costume manly and free, his face sunburnt and bearded, his postures strong and erect, his voice bringing hope and prophecy to the generous races of young and old. . . . If health were not his distinguishing attribute, this poet would be the very harlot of persons" (18).

Fig. 1. Whitman in July, 1854, at the age of 35.

serve as volunteer nurse in the hospitals. This activity he carried on for 3 years, meanwhile holding various government positions and corresponding with New York papers. In the summer of 1863, when the hospital work appeared to be affecting his health, he decreased somewhat the number and length of his visits, but by the end of the war he computed that he had made six hundred visits, seeing over eighty thousand sick and wounded soldiers.

After the war Whitman stayed on in Washington, working as a clerk in government offices and writing and publishing new editions of *Leaves of Grass*. In 1873, at the age of 54, he suffered a severe paralytic stroke. When he had partially recovered, he set out for the Jersey coast to avoid the summer heat of Washington, but broke down in Philadelphia and was taken to the home of his brother George in Camden. In this town he spent the greater part of his remaining years, at first with George, then in his own home on Mickle Street. Here he prepared further editions of the *Leaves*, the chief being those of 1881–1882 and 1891–1892. For long periods he was an invalid, confined to his room; at times he was stronger and able to travel, to the West, to Canada, to Boston and New York. During these years his literary reputation, which had received its first real impetus from his recognition by English literary lights in the sixties, grew ever wider, though his poetry was not to receive general acceptance until the twentieth century. He had a small coterie of fervent admirers, among whom was the Canadian physician, Richard Maurice Bucke, who first visited Whitman in July, 1877, and became one of the poet's closest friends as well as his principal medical adviser. After an illness of four months' duration, Whitman died on the 26th of March, 1892.

CASE SUMMARY

Family History (5)

Father. Walter Whitman (1789–1855). Died after an exhausting illness of nearly 3 years from paralysis. His death was "easy and unconscious."

Mother. Louisa Van Velsor Whitman (1795–1873). Her letters to Walt in the sixties complain often of "lameness in the right arm," which was "swollen and painful" (arthritis?), also of "dizziness in my head," "soreness and distress in my side," and "bad coughing" (November 19, 1867). Cause of death unknown.

Brother. Jesse Whitman (1818–1870). Had cardiovascular and central nervous system syphilis. In the last few years of his life became violent and was judged insane. He was confined to King's County Lunatic Asylum, Brooklyn, New York, where he died of "rupture of an aneurism."

Sister. Mary Elizabeth Whitman Van Nostrand (1821–1899). Had arthritis. Cause of death unknown.

Sister. Hannah Louisa Whitman Heyde (1823–1908). Was considered psychoneurotic. In 1892 had a mild paralytic stroke. Died in her 85th year of "pulmonary edema, mitral insufficiency, valvular disease of the heart and chronic nephritis."

Infant. Born April, 1825—died September, 1825. Cause of death unknown.

Brother. Andrew Jackson Whitman (1826–1863). Had a chronic disease of the "throat and bronchia" which probably was tuberculosis. Walt lived in the same house with Andrew until shortly before he left for Washington in 1862.

Brother. George Washington Whitman (1829–1901). In 1865 after George returned from the Army he was very sick for a time with "lung fever." During 1865 he had "headaches and face was bloated for a time." He also had rheumatic pains in his legs and hips. In 1899 George was sick and paralyzed.

Brother. Thomas Jefferson Whitman (1833–1890). Died of "typhoid pneumonia" (tuberculosis?). Jeff married Martha E. Mitchell (1859), who died in 1873 of tuberculosis. Walt had close contact with Jeff and his wife until he left for Washington.

Brother. Edward Whitman (1835–1892). Eddie was never normal. Apparently he had a birth injury which left him with a "crippled left hand and a paralyzed leg." "At the age of three he had scarlet fever which left severe after effects." He was also feeble-minded and an epileptic. He died in Blackwood Sanatorium, New Jersey, of "valvular heart trouble."

Marital history

Walt never married although, according to his own statement, he had several illegitimate children (3, 14).

Past history

In his youth Walt presumably had no serious illnesses. "I develop'd (1833–4–5) into a healthy, strong youth

(grew too fast, though, was nearly as big as a man at 15 or [illegible]." "The years 1846, '47, and there along, see me still in New York city, working as writer and printer, having my usual good health. . . ." (16). His "usual good health" continued until about 1858 when he suffered from a "sunstroke" (17); the details of this illness are unknown but it probably was the first of a subsequent series of minor strokes. He recovered, apparently uneventfully, and continued well except for colds. In April, 1863, he wrote his mother, "I weigh about 200, and as to my face (so scarlet) and my beard and neck, they are terrible to behold. I fancy the reason I can do some good in the hospitals among the poor languishing and wounded boys, is, that I am so large and well—indeed like a great wild buffalo, with much hair" (19).

Except for numerous colds accompanied by slight deafness, Walt remained fairly well until June, 1863, when he complained of "quite an attack of sore throat and distress in my head" (18). In July, 1863, while assisting at the amputation of a gangrenous limb of a Virginia Union soldier to whom he was much attached, he sustained a cut on the right hand. His hand became inflamed and swollen, and red streaks ran up to the shoulder (10). The infection subsided in approximately 4 to 5 weeks but left him so extremely weak and debilitated that he was advised to desist from his hospital visits for a while. He improved rapidly and on August 11, 1863, was again able to write his mother that he felt better than he had in 6 weeks. "About the wound in my hand and the inflammation, etc., it has thoroughly healed. . . ." (19). During the summer of 1863 Walt began to complain that the sun affected him, causing "aching and fulness on the head" (17). He resumed nursing the soldiers, however, and in January, 1864, was "well and fat" and weighed "about 206." He continued to complain of "fullness of the head," particularly in hot weather, and "spells of deathly faintness." He was again advised that he had "continued too long in the hospitals" and that he should not go "inside the hospitals for the present" (19). His spells continued with increasing frequency until finally, in July, 1864, he was "prostrated." Following this rather severe attack the "unconscious and perfect health" he "formerly had" was gone. It was his "first appearance in the character of a man not entirely well" (14). His spells persisted and in August and September, 1869, he had another severe attack which left him "prostrated and deadly weak," with little use of his limbs (13). He recovered satisfactorily and except for numerous severe colds remained well apparently until 1872, when he began to complain again of those "spells in the head" which had troubled him at intervals since 1864, and on January 24, 1873, he awoke to find himself paralyzed on the left side. He was placed under the care of Dr. W. B. Drinkard[2] of Washington, D. C., who gave him general supportive treatment, followed later by electric stimulation to his paralyzed side.

[2]William Beverly Drinkard (1842–1877) was born in Williamsburg, Virginia, the son of William R. Drinkard, Assistant Secretary and later acting Secretary of War under Buchanan. He received his education at Georgetown College, Washington, D. C., and the Lycée Imperiale, Orleans, France. In November, 1861, he began the study of medicine at Paris. Here he assisted in Desmarres Clinic where he studied principally diseases of the eye. He studied also under such other eminent teachers of the time as Velpeau and Flourens. In July, 1865, he went to London for several months and in the autumn of the same year returned to Washington where he entered the National Medical College, from which he received the M. D. degree in March, 1866. In 1872 he was elected professor of anatomy at the National Medical College, a post he held until his premature death 5 years later. Although trained in ophthalmology he did not confine himself to this specialty but engaged in the general practice of medicine. He was one of the founders of Washington Children's Hospital. (8)

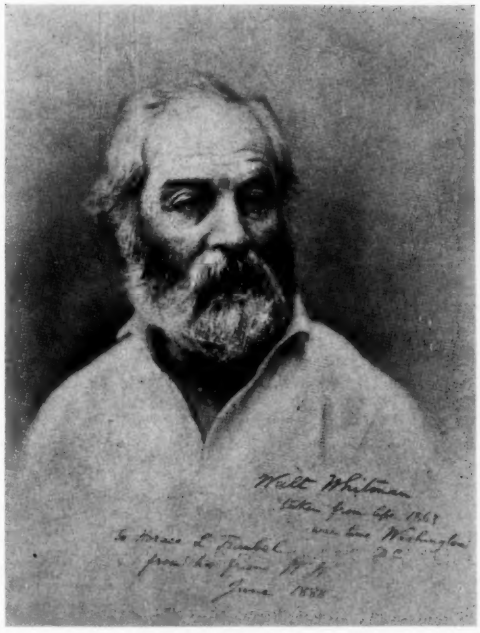

Fig. 2. Whitman at 44, in 1863.

After he had recovered sufficiently Walt started for the New Jersey shore to recuperate but broke down in Philadelphia and had to be taken to the Camden home of his brother George (10). Apparently Walt asked Dr. Drinkard to send his case report[3] to Dr. Matthew Grier[4] of Philadelphia, whom he saw several times.[5]

[3]Dr. W. B. Drinkard to Dr. Matthew Grier; Washington City, July 24, 1873; autograph letter in the Trent Collection, Duke University Library (15). The letter reads as follows:

My dear Doctor—

I am informed by M[r] Whitman, lately a patient of mine, now on a visit to Camden, that he intends to avail himself of your counsel and treatment before returning to this city: and he requests me to let you have a short statement of the history of his case up to the present time. It may be briefly stated, thus: On the 23d of January—? February—last M[r] W.—previously in good health—was attacked with left hemiplegia, presenting all the symptoms of such conditions, though none of them very marked at any time. Speech was hardly appreciably impaired: facial distortion very slight, & deviation of tongue just perceptible: left upper extremity never wholly useless: left lower showing the paretic condition more than any other part or organ. Constipation, slight at onset of attack, has required little attention subsequently.

Under the influence of rest, and such incidental treatment as was demanded from time to time, his general condition has slowly improved: locomotive power having, however, been only imperfectly regained. His principal annoyance has been a recurrent headache, with tendency to nausea—never actually reaching the latter point [preceding ten words cancelled by Drinkard].

After subsidence of everything like active manifestations, I commenced, cautiously, the use of the induced Current—with Gaiffe's battery,—and continued it for a number of weeks, without apparent result, beyond a decided improvement in nutrition of the lower limb. When he was on the point of leaving, I sug-

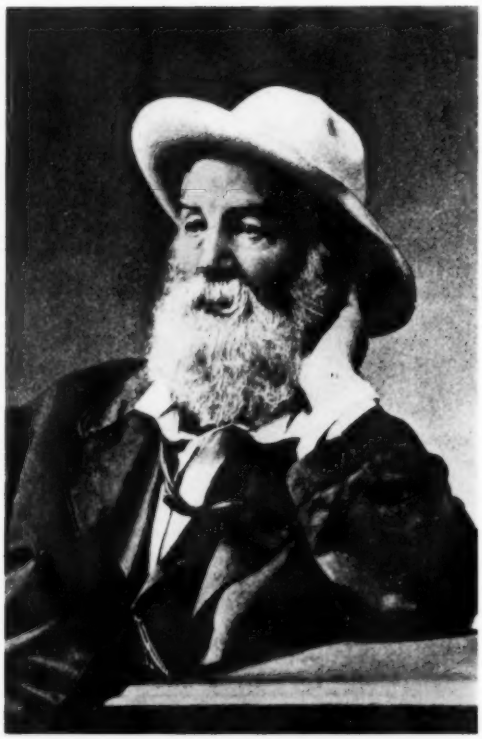

Fig. 3. Whitman at 53, in 1872.

gested to him the *possible* benefit to be derived from the use of the continued current: and I think it is with reference to that more particularly that he wishes to consult you.

M[r] Whitman's physical mould, his habits of life, tastes & mental constitution, are, I think, the most *natural* I have ever encountered: and as far as those things go, he has all in his favour. Beyond this, the prognosis is, of course, of the stereotyped uncertainty characteristic of such cases. He has occasionally taken pot. bromide & sod. bromide for his headaches: for a short time took the phosphates of iron, quinia & strychnia: Semi-occasionally, a mild laxative:—no other drugs that I recollect.

Hoping that you may be able to help M[r] Whitman in regaining the bodily independence on which his usual mental hopefulness very much depends, I am, my dear Doctor,

Very truly Yours
W[m] Bev. Drinkard

[4]Matthew J. Grier (1838–1900) was born in Philadelphia of Scotch-Irish ancestry. He received his M.D. degree from the University of Pennsylvania in 1803 (8).

[5]An incomplete manuscript note by Whitman (15) concerning a visit to Dr. Grier is of interest here: "June 2, '74 visited Dr. Grier again today at 312 S. 12th st. Phil. for consultation.

"He reiterated his theory that my sufferings (later ones), come nearly altogether from gastric, stomachic, intestinal, non-excretory, &c. causes, causing flatulence, a very great distension of the colon, fill'g of passages, weight on valves, crowding & press'g on organs, (heart, lungs, &c) and the very great distress & pain I have been under in breast left side, & pit of stomach, & thence to my head, the last month. Advised me by all means to begin the use of an injecture syringe, (Fountain No. 2, tepid water for clysters)—was favorable to my using whiskey—advised assaf-[oet]ida pills. 202—Kneading the bowel"

Under Dr. Grier's care[6] Walt improved gradually, but in July, 1885, had another attack which left him a year later "scarcely able to get up and down stairs" (3). It was at about this time that Dr. William Osler at Dr. Bucke's request paid Walt a professional visit. The poet had recovered from his paralytic attack of 13 years before and had only a slight residual weakness in his left leg. After a careful examination Osler told Walt that "the machine was in fairly good condition considering the length of time it had been on the road" (12, 7).

Whitman's fairly frequent "sick spells" during the late seventies and early eighties culminated in June, 1888, in another severe paralytic stroke. Bucke, who happened to be in Philadelphia at the time, took Osler with him to see Walt. They "found him in bed, conscious but mentally confused and with the speech slightly blurred and indistinct. There was no fever and the pulse was good. He had had one or possibly two attacks of transient unconsciousness with difficulty in speaking such as we now know are not uncommon with sclerosis of the arteries of the brain. For a week or more the condition looked doubtful, but he gradually improved and recovered without any permanent paralysis or loss of speech" (7).

Although Walt appeared to have recovered from this attack satisfactorily, his course continued down hill. In addition to his usual complaints of headache, lassitude and inertia, for the first time he began to complain of "indigestion" and "bladder trouble" (see Review of Systems). On March 18, 1891, Dr. Bucke asked Dr. Daniel Longaker[7] of Philadelphia to see Walt professionally. He found Walt an old man who complained of constipation, lack of energy, "inertia," urinary frequency and urgency. His apparent age was greater than his real years. Remote memory was better than recent. He moved about awkwardly with the aid of his cane. Muscular strength in the upper extremities was normal and sensation was not impaired. Heart and lungs were in good condition with little sclerosis of temporal or radial arteries.

Walt was treated expectantly with massage, laxatives, and catheterization[8] but continued in poor health until the onset of his Present Illness in December.

Review of Systems

Head. See Past History.

Eyes. Walt did not wear glasses and apparently had good vision until late in life.

[6]The following notes (15), written by Dr. Grier, indicate the treatment administered to Whitman:

R/Syr Calc lactophosph ℥ 1/10
Sig ½ teaspoonful after
breakfast & dinner
8-1-73 Grier
R/40153
Sodae lactatis ℥p
Glycerineae ℥ T
M. Sig. Teaspoonful after
each meal
5-6-74 Grier

descending secondary currents of Electro-Magnetism to lower limbs—none to the upper. *treat each* muscle seperately, For the brain—Inverse constant current say about 6 to 10 Daniells cells from each sciatic N. to sacrolumbar region, *not any higher under any circumstances. Every other days.*

[7]Dr. Longaker is still living in Philadelphia. In a personal letter to the author Dr. Longaker reminisces about Walt's last illness but cannot recall any details not already recorded in his article, "The Last Sickness and Death of Walt Whitman" (4).

[8]Dr. Longaker showed Walt how to catheterize himself with a soft rubber catheter. "He. . . . expressed surprise that the operation was so easy and painless. No arguing or coaxing was required, as is almost always necessary when this procedure is instituted" (4).

Ears. Except for occasional episodes of deafness associated with severe colds, hearing was good.

Nose, pharynx, tonsils. Frequent colds and sore throats: see Past History.

Mouth. Negative.

Teeth. No record of his ever having visited a dentist.

Heart. Negative.

Lungs. During the years 1863 to 1865 while nursing the sick and wounded in Washington, Walt was constantly exposed to "lung diseases" (19). In April, 1890, he had a "severe attack of the grip' which "sometimes almost strangles me" (3). In March, 1891, he had some slight trouble in his upper respiratory tract which he called his "mild attack of grip" (4). At no time did he complain of cough, dyspnea, wheezing, hemoptysis, or chest pain.

Abdomen. See Present Illness.

Gastrointestinal. In December, 1873, at the age of 54, Walt complained of "head troubles, & stomach troubles, & liver troubles—the doctor thinks the latter the seat & basis this time of all, or nearly all—head-swimming, faintness, vomiting, &c." (14). On May 22, 1874, "my being disabled and want of exercise for 16 months, (and many other wants too) have saddled me with serious dyspepsia and what the doctor calls gastric catarrh, very obstinate, causing me really more suffering and pain than my paralysis." In December, 1875: "these troubles" ["feeling of death and dizziness"], in the doctor's opinion "are from a very serious and obstinate *liver affection*—not from head, lungs, heart. . . ." (13). March, 1876: "I still have this baffling obstinate, apparently chronic affection of the stomachic apparatus and liver. . . . appetite sufficiently good, eat only very plain food. . . . digestion tolerable. . . ." (2). Jan. 21, 1891: "head, belly and bladder matters all in a bad way." March 16, 1891: "Obstinate long-continued horrible indigestion" (3). May 23, 1891: "The fiendish indigestion block continued" (14). Walt complained of obstinate constipation until onset of present illness. There is no mention of jaundice, characteristic gall-bladder pain, or intolerance to fatty foods.

Genitourinary: Dec. 3, 1888: "My physical trouble has veer'd quite entirely lately, or (more truly) added to, and is now that senile botheration from prostate or enlarged, or inflam'd gland (bladder business, diabetes) or other worse or less form of ailment. Dr. Osler was here this afternoon and is to bring over a surgeon on the 5th P.M., for more concise examination.[9] It has resulted the last four nights in quite no sleep. . . ." Dec. 4: "The gland suffering or whatever it is (the distressing recurrent stricture-like spasms, ab't from three to ten minutes almost continuously, the last five days and nights) has let up" (3). Jan. 21, '91: "head, belly and bladder matters all in a bad way." Mar. '91: Frequency, 20 times a day, nocturia, dysuria. (See Past History)

Venereal. Negative.

Neuromuscular. See Past History.

Extremities. See Past History.

Personal habits. In person Whitman was large and tall, above six feet. "He was in no sense a muscular man, an athlete. His body, though superb, was curiously the body of a child. One saw this in its form, in its pink color, and in the delicate texture of the skin. He took little interest in feats of strength, or in athletic sports. He walked with a slow, rolling gait, indeed, moved slowly in all ways; he always had an air of infinite leisure" (1).

His usual weight was 200 pounds or more, but at the onset of the present illness was only 140 pounds. Although temperate in the use of alcohol, he was not a total abstainer. He was inclined to eat excessively. He did not use tobacco.

[9] On his next visit Osler brought with him a Dr. Wharton; there is no record of their joint opinion on the case (11).

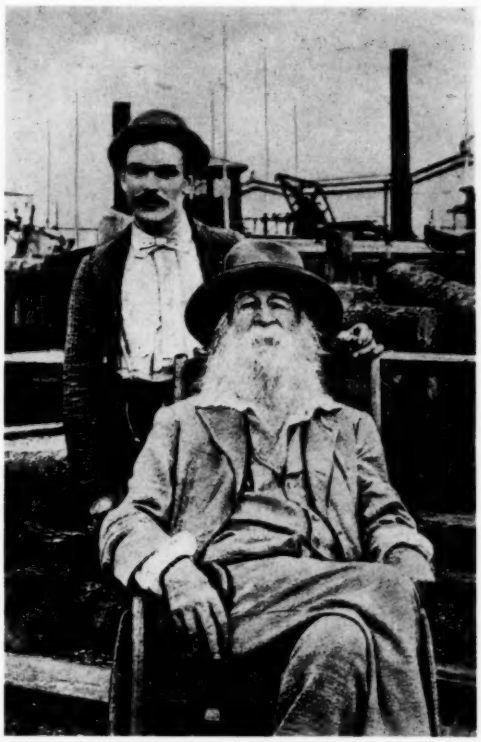

Fig. 4. Whitman with his nurse Warren Fritzinger, in July, 1890.

Present Illness (4, 6)

Walt was in his usual health until the afternoon of December 17, 1891, when he had a severe shaking chill followed by a rise in temperature (102°). This was accompanied by slight hoarseness and a cough productive of mucopurulent sputum. There was complete loss of appetite and marked prostration.

Course of illness. Dr. Longaker saw the patient 24 hours after the onset of the illness. At that time he found areas of dullness over both lungs, particularly on the right. The following day, the third of his illness, the areas of dullness had increased, especially over the right lung. It was thought he had a widely diffused bronchopneumonia. The lungs were poorly aerated and there were "hints of heart failure." On the fourth day Dr. Alexander McAlister of Camden was called in consultation so that a doctor could be immediately available in case of a sudden change for the worse. Walt showed no improvement and a tracheal rattle and cyanosis were noted. On December 22nd irregularity of the pulse developed. The following day the irregularity was more marked. Somnolency and cyanosis continued. Dec. 24: Extensive involvement of the left lung was found, with the right practically useless. There was marked cyanosis, labored respirations, and a rapid weak, and irregular pulse. Dec. 26: Walt appeared semiconscious but could be roused easily. The heart was still

irregular and intermittent. Dec. 27: A careful examination of the chest revealed some resonance on percussion and faint breath sounds, bilaterally posteriorly. The "left side [was] more impaired than we had believed." The respiratory movements were rapid and entirely abdominal. Mucopurulent expectoration continued. The cough, prominent from the beginning, was greatly accentuated when Walt lay on his right side. There was little if any fever. Weight loss was evident. By December 29th, when it became clear that the illness was to be protracted, a professional nurse, Mrs. Elizabeth Keller, was engaged.

Slight improvement occurred and continued, and by January 7, a normal pulse and respiration ratio was reestablished, 72/18. During the previous year "the pulse [was] very uniformly at sixty-four." All alarming symptoms abated, and Walt settled down to a routine of life little varied to the end. He frequently complained of pain and soreness in the left side, splenic region, and later severe pain in the left foot. On January 20 a fine rash was discovered on his abdomen and chest. On March 9th Longaker records: "P-90, R-20 rather shallow and when lying on back almost entirely abdominal. Traubel informs me that immediately the position on the right side is assumed he has a profuse expectoration attended by cough. Probably a bronchiectatic cavity which partly empties." And on March 11th: "P-80 R-22 mostly abdominal. Making a superficial examination of anterior surface of chest I found mucus râles on left side—vesicular murmur on right side scarcely audible—bronchial breathing instead. Heart sounds at apex faint, first scarcely heard—over aortic cartilage and pulmonary the second sound only can be heard. Impairment of resonance on right side—good on left."

Hiccough began shortly after onset of the present illness and except for brief intervals was a persistent symptom until the end. Night sweats occurred only late. After the initial attack fever, "if present at all," was very moderate. There was persistent weight loss. If Walt lay on his left side he had severe pain in that side and if on the right side he coughed constantly and the "phlem choked him." Hourly or oftener he would ring or call the nurse to change his position. Soon it was possible for him to lie on the left side only, and finally even this tortured him. Toward the end he had occasional urinary and fecal incontinence. A few days before his death an ecchymotic area was found over his left flank.

On March 23, 1892, his dyspnea increased and his pulse again became faint and irregular. He died quietly on March 26th.

Autopsy

The account of the autopsy given by Dr. Longaker (4) may be quoted at length: "The following are the notes of the post-mortem performed on the body of Walt Whitman, March 27, 1892, by Henry W. Cattell, demonstrator of gross morbid anatomy, University of Pennsylvania. The autopsy was made in the presence of Dr. Daniel Longaker, Prof. F. X. Dercum, Dr. Alexander McAlister, and Horace L. Traubel.[10] The brain was removed by Dr. Dercum, and is now, after having been hardened, in the possession of the American Anthropometric Society.[11] This Society, which has been organized for the express purpose of studying high-type brains, intends to first photograph the external surfaces and then make a cast of the entire brain. After this, careful microscopic observations will be made by competent observers.[12]

"Both the head and the brain were remarkably well formed and symmetrical. The scalp was thin, and practically no blood was lost when the incisions were made. The calvarium was white and the muscular tissue pale. The dura mater was very adherent to the sull cap and showed recent pachymeningitis on both sides, but especially on the right. The blood in the longitudinal sinus was fluid. The bone was well ossified, and there was little or no diploic substance remaining. The pia and arachnoid were very oedematous, and considerable cerebrospinal fluid escaped during the removal of the brain. Numerous milky patches, especially over the vertex, were seen, but no miliary tubercles were discernible. The membranes were not adherent to the cortex, and the brain substance was excessively soft. The blood vessels of the circle of Willis were very slightly atheromatous. The brain weighed forty-five ounces, two hundred and ninety-two and one-half grains avoirdupois. . . .

"The body was emaciated, postmortem lividity was slight, and there was no rigidity. On attempting to remove the skin of the left side a little to the left of the median line at the sixth rib laudable pus escaped. On careful examination there was found here an elevated area the size of a fifty-cent piece, which was situated over but slightly to the left of the center of the manubrium and had eroded that bone to the extent of a twenty-five cent piece. The abscess had burrowed into the pectoralis major and had commenced to erode the superficial fascia. It had not broken inwardly, though it could be plainly seen from the posterior surface of the sternum.

"About half an ounce of pericardial fluid was found. The heart, which weighed about nine ounces, was very flabby and well covered with epicardial fat, except a small portion in the center of the right ventricle. The pulmonary valves were slightly thickened but competent. Aortic valves in good condition, closing completely. The mitral valves good, the tricuspids perfectly good.

"There were three and one-half quarts of serous fluid in the left pleural cavity, and the lung, the size of the hand, was completely pressed against the mediastinum, so that it was absolutely impossible for air to enter. A few bands of recent lymph extended across an injected pleura, which was hemorrhagic in spots.[13] On the pleural surface at a point just below the nipple was an abscess the size of a hen's egg, which had completely eroded the fifth rib, the longest diameter of the abscess being in the vertical direction. There was no external mark on the skin to lead one to suspect the presence of the abscess, though there was some bulging and distinct fluctuation, and the two ends of the rib could be plainly felt grating against each other. Only about one-eighth of the right lung was suitable for

[10] "Mrs. Davis, Walt's housekeeper, was much opposed to the postmortem examination of Mr. Whitman's body. Of course, she had no legal right to object. Mrs. George Whitman was consulted as to this, and, it was understood, consented. During the postmortem (it was in the back parlor), I detected the odor of a fearful pipe. It might have been from the street and it might not have been. Mr. Whitman was not smoking, I was sure" (2).

[11] "The American Anthropometric Society was established in 1889 at a meeting which took place at the residence of . . . . . The founders were: Harrison Allen, Francis Xavier Dercum, Joseph Leidy, William Pepper and Edward Charles Spitzka. The chief object of the society was the preservation of the brains of its members. . . . In the order of acquisition, the list of brains in the collection included the following: (1) Joseph Leidy, (2) Philip Leidy, (3) J. W. White, Sr., (4) Andrew J. Parker, (5) Walt Whitman, (6) Harrison Allen, (7) Edward D. Cope, (8) William Pepper" (9).

[12] "The brain of Walt Whitman, together with the jar in which it had been placed, was said to have been dropped on the floor by a careless assistant. Unfortunately, not even the pieces were saved. . . ." (9).

[13] "This pleurisy was due to deposit in the membrane of tubercles, the same as were found about the spleen and the peritoneum of the left side of the abdomen in general" (Longaker's comment).

breathing purposes. The upper and middle lobes were consolidated and firmly bound down to the pleura. There were about four ounces of fluid in the cavity. Large tubercular nodules and areas of catarrhal pneumonia were everywhere to be found. Those portions of the lung not tubercular were markedly emphysematous, this being especially marked at the free edges of the lung.

"The spleen was soft and weighed about eight ounces, the capsule thickened and fibrous; on section pulpy. It was matted down to the diaphragm and showed only peritonitis and peri-splenitis. Numerous tubercles occupied this region, extending to the anterior wall of the stomach and to all of the neighboring viscera. The diaphragm was pushed downward by the fluid.

"The kidneys were surrounded by a mass of fat. The left suprarenal capsule was tubercular and contained a cyst the size of a pigeon's egg. In this was found a darkish fluid. The capsule strips readily; the kidney weighed about six and one-half ounces, and showed some parenchymatous change. The kidney substances were soft, red, and swollen, and somewhat granular. The right kidney was a little the smaller and the better of the two.

"The liver was about normal in size, though fatty and contained an extra fissure near the center. Some tubercles were observed.

"A huge gall stone almost entirely occupied a rather small gall bladder to which it was firmly adherent. The outer surface of the stone was covered with a whitish deposit.

"The pancreas was hemorrhagic. The common iliacs were but very slightly atheromatous.

"Over the whole of the mesentery, especially in its lower portion, were hundreds of minute tubercles varying in size from that of a fine needle-point to the head of a good-sized pin. These whitish points were surrounded by a hemorrhagic base. The serous surface of the intestines was injected and dotted with tubercles. The bladder was empty and the walls thickened. The prostate was enlarged. The rectum was swollen and filled with semi-fluid feces. A few hardened masses were found in the transverse colon. The stomach was small. The vermiform appendix was two inches long and patulous, containing two small hardened fecal masses of an irregular outline. The sigmoid flexure was unusually long.

"The above macroscopic lesions of the various organs were confirmed by microscopic sections.

"It would seem very probable that the extensive adhesion of the dura mater to the calvarium was due to an old sun-stroke.

"The cause of death was pleurisy of the left side, consumption of the right lung, general miliary tuberculosis and parenchymatous nephritis. There was also found a fatty liver, gallstone, a cyst in the adrenal, tubercular abscesses, involving the bones, and pachymeningitis."

COMMENT

The autopsy is exasperatingly incomplete, and from the available facts it is difficult to reconstruct the exact sequence of events which led to Walt's death. However, it is sufficiently inclusive to allow us to revise the diagnosis to conform with our present-day concepts of pathology.

Did Whitman really have tuberculosis? Could he have had cancer of the prostate with terminal spread or a primary cancer of the lung? Tuberculosis was well recognized by 1892[14], however, and

[14]Koch's work on the tubercle bacillus was done in 1882.

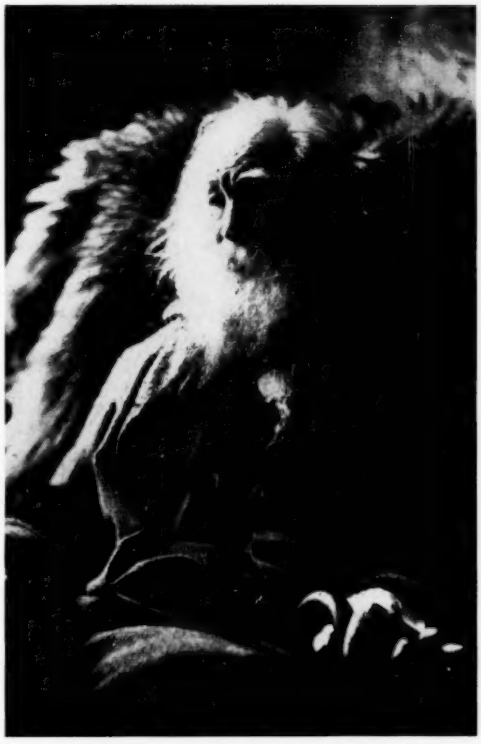

Figure 5. Whitman at 72, 1891.

since the autopsy was performed by some of the best American pathologists of the day, we are reasonably safe in accepting their diagnosis.

Judging from the extensive involvement of the right lung, "the upper and middle lobes were consolidated and firmly bound to the pleura," the tuberculous process was of long duration, probably years. Unfortunately, no mention is made of the left lung other than that "it was completely pressed against the mediastinum." The apparent long duration of the pulmonary lesion with no antecedent history of cough, dyspnea, chest pain or hemoptysis is nothing short of remarkable. Walt was exposed to members of the family with tuberculosis for several years before he left for Washington in 1862, at the age of 43, but it was precisely at this time that he was proclaiming his excellent health. During his Washington hospital days, also, he must have been exposed to much tuberculosis among the soldiers. However, in his frequent references to his illnesses of this period there is no mention of pulmonary compli-

cations. The tuberculous pleural effusion on the left probably had been present some months before his terminal illness and could have been secondary to extension through the parietal pleura of the chest wall abscess or the rupture of a small tuberculous node.

At the onset of his last illness the infected pleural fluid, which could have been responsible for the sudden chill and fever, must have ruptured into a bronchus, for there was profuse expectoration of mucopurulent sputum at the onset, something entirely new for Walt. This profuse expectoration, which was greatly accentuated when he lay on his right side, persisted until his death. Sufficient drainage of the left chest through the bronchus must have occurred to produce the slight symptomatic improvement noted early in the course of his last illness. The fluid on the left was not diagnosed antemortem because the doctors did not wish to subject Walt to the discomfiture of a complete examination. The presence of a bronchopleural communication on the left is further borne out by Dr. Longaker's examination of the anterior surface of the chest on March 11th, when he found "impairment of resonance on right—good on left," indicating that there was air in the left pleural space and not in the lung, since the autopsy showed the lung to be collapsed against the mediastinum.

The tuberculous abscesses of the sternum, rib and chest wall and foot were old but their exact duration is difficult to estimate.

Numerous tubercles occupied the area around the spleen extending to the anterior wall of the stomach and all neighboring viscera including the left adrenal gland. No tubercles were found in the splenic pulp, and only a few were observed in the liver. The mesentery and intestine, particularly the lower portion, were covered with minute tubercles. This certainly is not the picture of a miliary spread via the blood stream but rather that of a direct dissemination probably from an old focus around the spleen, a lesion which may have been of the same vintage as the abscesses described above and which undoubtedly accounted for the hiccough and severe pain in his left side.

The left adrenal cyst indicated an old process and may have been in part responsible for the "lassitude and inertia" Walt complained of for many years. No mention was made of the right adrenal gland.

Since careful examination of the brain was not carried out we have no record of old areas of destruction which might have been present, but we do have the autopsy findings of extensive cerebral atrophy. In spite of marked wasting of the brain described at the postmortem examination, Walt's mind continued active and keen to the last[15] although his memory had begun to fail.

His long-standing symptoms of indigestion, nausea, and constipation can be attributed to the chronic cholecystitis and cholelithiasis.

His urinary symptoms arose from the urethral obstruction secondary to hypertrophy of the prostate.

Did Walt have hypertension or perhaps a labile blood pressure secondary to vasospasm? This, of course, would have been an antemortem diagnosis if his blood pressure could have been measured.[16] In favor of such a condition are his ruddy complexion, frequent severe headaches and feeling of fulness in the head, and the numerous slight to severe cerebral insults suffered after 1858. However, in hypertension of such long standing we should expect more advanced arteriosclerosis and cardiac hypertrophy.

Our revised and final diagnosis should read, then: Pulmonary tuberculosis, far advanced, right; atelectasis of left lung; tuberculous empyema, left; bronchopleural fistula, left; disseminated abdominal tuberculosis; tuberculous abscesses of sternum, fifth rib and left foot; cyst of left adrenal gland; chronic cholecystitis and cholelithiasis; cerebral atrophy; cerebral arteriosclerosis; benign prostatic hypertrophy; pulmonary emphysema; cloudy swelling of kidneys; history of hypertension (?).

In an age of psychiatry no discussion of Whitman's medical history would be complete without some mention of that very controversial subject of his sexuality. Was he homosexual? At this late date an unassailable answer is unlikely, although after a study of his life, personality, habits, and writings, one fact stands out clearly: by no standards could Whitman's attitudes and behavior toward sex be considered "normal." Yet the charge of homosexuality has never been proved. John Burroughs, a friend of long standing, described Walt as in "no sense a muscular man, an athlete. His body, though superb, was curiously the body of a child. One saw this in its form, in its pink color, and in the delicate texture of the skin" (1). Perhaps this is the real clue to the personality of the man who embraced all mankind, man and woman alike. Could he have been eunuchoid?

[15]Last revision of *Leaves*, 1891–92.

[16]Sphygmomanometry was introduced in the late 19th century.

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17. Idem. Walt Whitman and the Civil War. Philadelphia: University of Pennsylvania Press, 1933.
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REVIEWS OF NEW BOOKS

IN the opening chapter of *Erkrankungen des uropoetischen Systems und der Prostata durch Störung der Blutströmung*[1] by Hutter, the author favors humoral pathology of living tissues over the cellular pathology teaching of Virchow. In his opinion humoral pathology gives a more rational explanation of normal and abnormal body cells. Increase and growth of tissues result from substances brought to it by the blood stream. In malignancies, for instance, there is a battle between the blood ingredients going to normal and tumor cells. Many writers are quoted endorsing the new views of disease and pathological cellular changes. Hutter contends that laboratory examinations and procedures, while important, can never give an accurate clinical estimate of the patient's health and prognosis.

In prostatic hypertrophy the author states that there is a hormonal imbalance with the male component predominating. Following surgery of the prostate Hutter believes that foreign hemostatic bodies and ligatures used to control bleeding promote wound infection and secondary hemorrhage. The wound reunion of the urethra and bladder with primary bladder closure tends to shorten the morbidity and wound healing. The prostatic bed can produce its own hemostasis and should not be interfered with too much by the surgeon.

Urinary calculi were more frequently noted in immobilized injured and wounded soldiers. Many autopsies and reports are quoted giving the incidence of urinary calculi in amputees and severely wounded. There was a much higher mortality in soldiers following nephrectomy for tuberculosis (25%) than in peacetime civilian practice (no deaths in 200 nephrectomies). The high mortality is attributed to war dislocations and shock.

The circulation in the presence of renal lesions (pyelonephritis, early arteriosclerosis, war nephritis, poisons) may be improved by removing the overacting vasoconstrictors (decapsulation).

The lesser grades of nephroptosis seldom cause hydronephrosis and infection. Mild cases should be treated conservatively. Advanced cases respond to surgery and nephropexy.

There is an interesting discussion on scoliosis, kyphoscoliosis, lordosis, and resulting impairment of renal function. The difference in renal and ureteral displacements on the convex and concave sides are carefully noted and illustrated with drawings and roentgenograms.

This compend is a good postwar review of urologic subjects and problems. Infectious urology is not included. There is no mention of the newer therapeutic agents as penicillin or streptomycin.

LEANDER W. RIBA

THE first edition of *Fundamentals of Psychiatry*[2] by Edward A. Strecker appeared in 1942. In the fourth edition, the text has been revised once again. The author has added a chapter on psychosomatic psychiatry as well as two suggested nomenclatures for classification. There are chapters also on etiology, methods of examination, and symptoms, organic and toxic psychoses, functional psychoses and psychoneuroses, psychiatry and war, and psychiatric nursing, and finally there is a glossary and an index. The style is clear, terse, firm, and often distinguished by dry wit. Diagrams are offered to represent the author's conceptions for elementary students. His extensive experience is often evidenced and his grasp of the somatic aspects and accompaniments of mental disease. His general approach agrees with that of Adolph Meyer, well known as psychobiology (cf.p. 34). The name of Freud appears only twice, when he speaks of Freud's "hypothesis of the 'id'" (p. 172), and of Freud's conception of neurasthenia (p. 238). However, the influence of Freud can be traced on numerous pages when the author gives his own views, for example, on "conversion hysteria" and on paranoia and paranoid conditions. "In waking life and in sleep," he states (p. 106), "in its conscious, subconscious, and unconscious components there is unceasing mental activity." Like some other topics, treatment as a rule is little more than outlined in this book. Nevertheless, the beginner in psychiatry and the doctor in other fields will find it most useful in acquainting him with the status of present day psychiatry.

EDMUND JACOBSON

THE great decline in the incidence and mortality from communicable disease in the United States during the past twenty-five years and the introduction of chemotherapy and antibiotic therapy has reduced the number of specialists skilled in the diagnosis and treatment of communicable diseases. In most instances these experts are principally found in cities of great population where the greatest number of cases occur. However, diagnosis, adequate modern treatment, and reporting of cases promptly to health authorities to increase speedy control are still a major responsibility of the general practitioner.

The need for authoritative reference based on up-to-date experience is now more essential than ever for the complete battle against the communicable diseases.

[1] ERKRANKUNGEN DES UROPOETISCHEN SYSTEMS UND DER PROSTATA DURCH STÖRUNG DER BLUTSTRÖMUNG. By Professor Dr. Karl Hutter. Vienna, Austria: Wilhelm Maudrich, 1947.

[2] FUNDAMENTALS OF PSYCHIATRY. By Edward A. Strecker, M. D., Sc.D., LL.D. Litt.D., F.A.C.P. 4th rev. ed. Philadelphia, London, and Montreal: J. B. Lippincott Co., 1947.

The second edition of *Handbook of Communicable Diseases*[1] by Dr. Franklin H. Top presents in a clear, concise, colorful and illustrative pattern the present day knowledge about each communicable disease which the family physician is called upon for consultation.

The 14 new chapters dealing with specific diseases and discussed by collaborating authorities enrich the value of the second edition of *Handbook of Communicable Diseases*. Newer problems such as primary atypical pneumonia, revision of nursing care, leprosy, management of communicable diseases in hospital, malaria, epidemic keratoconjunctivitis, leptospiral jaundice, ringworm of the scalp constitute additional information elaborated upon in the second edition.

This book deserves not only the intensive study of every medical student, but also should be part of the personal library of every general practitioner.

E. A. PISZCZEK

A SERVICEABLE aid to the medical student and a convenient source of graphic material for the postgraduate is presented in Professor Jamieson's *Illustrations of Regional Anatomy*.[2] The seven small volumes contain an ample series of pictures of gross anatomical structures. The booklets, however, have no accompanying text, contain no directions designed to guide a dissector. The legends are of the briefest order. The current edition and its predecessor contain an index.

The illustrations are grouped in compact volumes, in each of which the loose leaves are fitted on pillars; from these the sheets are easily removable for rearrangement in any sequence momentarily convenient to the reader. The pages are printed on one side only; the paper stock is unusually good. The 320 plates of illustrations cover the anatomy of the several subdivisions of the body: central nervous system, head and neck, abdomen, pelvis, thorax, upper limb, and lower limb. The head and neck are allotted the largest number of figures, the thorax the smallest number.

The brain is extensively illustrated; basal nuclei, motor and sensory areas are indicated diagrammatically, as are also the principal tracts, commissures, etc.; blood vessels, cerebral ventricles, and choroid plexuses are all presented in very arresting coloration.

The anatomical features of the head and neck are illustrated by drawings which include entire dissection fields, layer-by-layer dissections of individual sense organs, diagrams of nerve plexuses and of transverse and sagittal sections taken at crucial levels. Some of the figures might be baffling to a novice, since they do not indicate what has been excluded, or which layers have been removed to bring into view the stratum which the figure represents. Others lose value by being so diagrammatic that they merely suggest, but do not closely resemble, the particular group of structures as they appear in a dissected human body.

The booklet on the abdomen contains ingenious illustrations of the abdominal muscles and the inguinal canal, but some of them, in being utterly diagrammatic, sacrifice anatomical clarity to attain schematic vividness. The treatment of the inguinal region, mesenteries, blood vessels, kidneys, and suprarenals is highly conventional; the figures resemble museum models rather than dissections. The schematic drawings of the abdominal layers take considerable liberty with the true constitution of the parietal lamellae and laminae; they do record the common variations which are important in laparotomy and in hernioplasty.

In the volume on the pelvis and perineum, color is again profusely, but often helpfully, used. The author's order of plates is seemingly rather haphazard for a division of anatomy in which a knowledge of serial succession is of fundamental surgical importance. While the layers of the pelvic and urogenital diaphragms are shown in schematic clearness, they are not portrayed accurately. The relations of the pelvic viscera to their ligamentous, fascial, and diaphragmatic supports would be of little use in training critical students for the practice of gynecology, urology, or proctology.

In the set of plates which depict the anatomy of the thorax, the schematic method is utilized to greater advantage, since much of the important anatomy of the thoracic cage and of its visceral, vascular, and nervous contents may be taught from transverse and sagittal sections and from surface projections of organs.

In the sections on the upper and lower extremities, the figures which show the plaques of muscular attachment to the skeletal elements are fundamentally similar to those found in the standard textbooks, atlases, and manuals of gross anatomy. Here the order is the logical one of successive layers, from cutaneous nerves, superficial veins, and fascial sleeves, through progressively deeper layers of muscle. In the simpler figures, for example, those dealing with the synovial sheaths of the hand and foot, the schematic plan is utilized to great advantage; but when the same device is employed to show the tendons, nerves, vessels, and muscles, the collection of transected structures forms a somewhat overpowering assemblage.

The colors employed in the illustrations seem, upon first examination, to be needlessly garish. However, the reader soon becomes accustomed to their chromatic strength and learns to use the colors as so many signals.

Considered as a whole, *Illustrations of Regional Anatomy* is a useful adjunct to the student's regular anatomical library; it treats of the kind of anatomy

[1] HANDBOOK OF COMMUNICABLE DISEASES. Franklin H. Top, A.B., M.D., M.P.H., F.A.C.P. 2nd ed. St. Louis: The C. V. Mosby Co., 1947.

[2] ILLUSTRATIONS OF REGIONAL ANATOMY. By E. B. Jamieson, M.D. Section I—Central Nervous System; Section II—Head and Neck; Section III—Abdomen; Section IV—Pelvis; Section V—Thorax; Section VI—Upper Limb; Section VII—Lower Limb. 7th ed. Edinburgh: E. J. S. Livingstone, 1947; Baltimore: The Williams & Wilkins Co., 1947.

which is customarily presented in charts. Its graphic character, going beyond the limit set in the standard type of illustration, allows the set of books to function as a link between the regular atlas which the student uses at the dissection table and the blackboard drawings which so commonly enliven lectures in gross anatomy. For the familiar compends, digests, and summarizing handbooks of anatomy, these abundantly illustrated volumes would serve as ideal companions. BARRY ANSON

THE ninth revision of the popular textbook, the Ballenger *Diseases of the Nose, Throat, and Ear.*[1] remains one of the best introductions to otolaryngology for the student and practitioner. It is easily readable, clearly written for the most part, and its numerous illustrations are well selected and graphic. A wide amount of information is given which in the space allotted requires a somewhat dogmatic presentation. Moot points are on the whole adequately discussed and errors are few.

Considerable emphasis has been placed on operative procedures. While this may give the student a somewhat biased view it helps make the book valuable for reference as well as for an undergraduate text. From description and illustration, operative techniques are easily grasped. The method of describing operative procedures on the basis of historical development gives the student an understanding not otherwise attainable in many instances. In others it leads to the retention of perhaps an unnecessary amount of deadwood.

Latest advances in the specialty are well covered. A new chapter has been added on headaches and neuralgias of the face and head and up to date revisions are given on the labyrinth, endoscopy, and the operative relief of laryngeal paralysis by authorities in those fields. The format is good, the paper and printing excellent, and the volume maintains its previous high standing. T. C. GALLOWAY

[1] DISEASES OF THE NOSE, THROAT AND EAR. By William Lincoln Ballenger, M.D., F.A.C.S., and Howard Charles Ballenger, M.D., F.A.C.S. Assisted by John Jacob Ballenger, B.S., M.D. 9th ed. Philadelphia: Lea & Febiger, 1947.

BOOKS RECEIVED

Books received are acknowledged in this department and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

THE 1947 YEAR BOOK OF NEUROLOGY, PSYCHIATRY AND NEUROSURGERY. NEUROLOGY edited by Hans H. Reese, M.D., and Mabel G. Masten, M.D. PSYCHIATRY edited by Noland D.C. Lewis, M.D. NEUROSURGERY edited by Percival Bailey, M.D. Chicago: The Year Book Publishers, Inc., 1948.

HUMAN PHYSIOLOGY. By F. R. Winton, M.D., D. Sc., and L. E. Bayliss, M.D. 3rd ed. Philadelphia, Toronto: The Blakiston Co., 1948.

PHYSICAL TREATMENT OF INJURIES OF THE BRAIN AND ALLIED NERVOUS DISORDERS. By K. M. Hern. With a Foreword by Air Vice-Marshall Sir Charles P. Symonds, K.B.E., C.B., D.M., F.R.C.P. Baltimore: The Williams & Wilkins Co., 1947.

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CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

ARTHUR W. ALLEN, Boston, *President*
DALLAS B. PHEMISTER, Chicago, *President-Elect*

PRELIMINARY PROGRAM FOR 1948 CLINICAL CONGRESS THE BILTMORE HOTEL, LOS ANGELES, OCTOBER 18 TO 22, 1948

PLANS are proceeding for the program of the thirty-fourth Clinical Congress of the American College of Surgeons which will be held in Los Angeles at the Biltmore Hotel, from October 18 to 22, 1948.

A preliminary schedule of clinics, preceded by a list of the hospitals which will participate and the names of the representatives who are responsible for the program at each hospital, was published in the June issue. Twenty-five hospitals have so far indicated a desire to participate, and they will arrange their programs to cover subjects in general surgery, obstetrics and gynecology, fractures, orthopedic surgery, thoracic surgery, neurosurgery, genitourinary surgery, and ophthalmology and otorhinolaryngology. During the Congress Daily Clinical Bulletins will be issued which will give the final clinical program.

It is expected that arrangements for telecasting operations from one or more of the hospitals will soon be ready for announcement. The use of television is especially desirable after the exceedingly successful demonstration of its teaching value at the Clinical Congress in New York last year.

The usual varied and comprehensive program of meetings at the headquarters hotel is planned. The opening session will be a General Assembly for both surgeons and hospital personnel, on Monday morning. Scientific sessions, official meetings, and hospital conferences will follow during the five day Congress. In addition to meeting rooms in the Biltmore Hotel, the Biltmore Theater and the spacious Philharmonic Auditorium across the street from the hotel will be used for the larger audiences. The capacity of the Philharmonic Auditorium is 2,700 and that of the Biltmore Theater about 1,700.

PRESIDENTIAL MEETING

The opening evening session of the Clinical Congress will be devoted to the Presidential Meeting, at which the officers-elect, consisting of Dr. Dallas B. Phemister of Chicago as president, Dr. Howard A. Patterson of New York as first vice president, and Dr. Carl H. McCaskey of Indianapolis as second vice president will be installed. Dr. Arthur W. Allen of Boston, outgoing president and vice-chairman of the Board of Regents, will preside and will deliver the Presidential Address. The third Martin Memorial Lecture will be delivered by Dr. Clarence Crafoord, Professor of Surgery, University of Stockholm.

CONVOCATION

The annual Convocation will be held on the final evening, Friday. The formal initiation ceremonies and the presentation of the Fellowship Address by Dr. L. A. Du Bridge, President, California Institute of Technology, Pasadena, will constitute the program. Dr. Du Bridge's subject will be "The Physicist Meets the Doctor."

EVENING SCIENTIFIC SESSIONS—GENERAL SURGERY

"Malignant Lesions of the Thyroid Gland" will be the subject of the Tuesday evening general surgery symposium. "Pathology" will be discussed by Dr. Frank W. Foote of New York; "Aberrant Thyroid" by Dr. Brien T. King of Seattle; "Malignancy in Nodular Goiter" by Dr. Warren H. Cole of Chicago; and "Radioactive Iodine in the Treatment of Thyroid Diseases Including Cancer" by Dr. Myron Prinzmetal, Los Angles.

"Endometriosis" will be the subject for the Wednesday evening general surgery symposium. "Significance of Endometriosis" will be discussed

by Dr. Joe V. Meigs of Boston; "Surgical Procedures Involved in the Treatment of Endometriosis" by Dr. Virgil S. Counseller of Rochester, Minnesota. A third paper will be presented on "Theories and Medical Treatment of Endometriosis." The annual Fracture Oration will also be presented at the Wednesday evening session.

"Surgery of the Heart and Great Vessels" will be the subject of the Thursday evening general surgery symposium. "Surgical Treatment of Pulmonic Stenosis" will be discussed by Dr. Alfred Blalock of Baltimore; "The Surgical Treatment of Constrictive Pericarditis" by Dr. Emile F. Holman of San Francisco; "The Surgery of Patent Ductus Arteriosus" by Dr. John C. Jones of Los Angeles; and "Treatment of Coarctation of the Aorta" by Dr. Robert E. Gross, Boston.

EVENING SCIENTIFIC SESSIONS—OPHTHALMOLOGY

The preliminary program for the Tuesday evening Ophthalmology session includes the following subjects: "Tumors of the Eyelids and the Conjunctiva", by Dr. Michael J. Hogan of San Francisco; "Partial Keratectomy," by Dr. George L. Kilgore of San Diego, and the third paper will probably be on "Studies of the Cytology of Conjunctival Exudates."

The Wednesday evening program will be devoted to a panel discussion on the subject, "Neoplasms of the Orbit and Nasal Accessory Sinuses" and will be participated in jointly by ophthalmologists and otorhinolaryngologists.

The program for the Thursday evening Ophthalmology session includes the following subjects: "Retinal Detachment," by Dr. Dohrmann K. Pischel of San Francisco; "The Use of Retrobulbar Alcohol Injection for Ocular Pain," by Dr. Alfred E. Maumenee of Baltimore, and the third paper is not yet definitely selected.

EVENING SCIENTIFIC SESSIONS OTORHINOLARYNGOLOGY

The preliminary program for the Tuesday evening Otorhinolaryngology session includes four subjects: "Effects of Streptomycin on Eighth Nerve Function," by Dr. Page Northington of Oakland; "Anatomical Considerations in Ear Surgery," by Dr. J. Brown Farrior of Tampa. A third paper will be on "Suspension Laryngoscopy" and there will be a fourth for which a definite title has not yet been determined.

The Wednesday evening program, as stated under "Ophthalmology," will be on the subject, "Neoplasms of the Orbit and Nasal Accessory Sinuses," and will be a joint session with the ophthalmologists.

The program for the Thursday evening Otorhinolaryngology session includes the following four subjects: "Tumors of the Nasopharynx," by Dr. Harry C. Rosenberger of Cleveland; "Modern Management of Oro-Antral Fistula," by Dr. Richard Thomas Barton of Beverly Hills; "Present Day Status of Fenestration Surgery," by Dr. Leighton F. Johnson of Boston; and a fourth paper will probably be on "Laryngeal Malignancy."

GENERAL SURGERY PANEL DISCUSSIONS

General surgery panel discussions will be held on Monday, Tuesday, and Wednesday afternoons, from 1:30 to 3:00 and from 3:30 to 5:00 o'clock, and on Thursday afternoon from 3:30 to 5:00. The early session on Monday will be on "Acute Renal Failure in Surgical Patients," with Dr. Frederick A. Coller of Ann Arbor as moderator, and the late session on "Tumors of the Mouth, Jaw and Face," with Dr. Gordon B. New of Rochester, Minnesota, as the moderator. The early session on Tuesday will be on "Low Lying Malignant Lesions of the Bowel," with Dr. Fred W. Rankin of Lexington, Kentucky, as moderator, and the late session on "Evaluation of Liver Function in Relation to Surgery," with Dr. Nathan A. Womack, Iowa City, as moderator. The early session on Wednesday will be on "Peripheral Arterial Disease" with Dr. Alton Ochsner of New Orleans as moderator, and at the late session "Ulcerative Colitis" will be discussed with Dr. Henry W. Cave of New York as moderator. The Thursday session will be concerning "Isotopes in Surgery" with Dr. George M. Curtis of Columbus as moderator.

OPHTHALMOLOGY PANEL DISCUSSIONS

Panel discussions in ophthalmology will be held Tuesday, Wednesday, and Thursday mornings from 9:00 to 10:30 o'clock. The Tuesday subject will be "Surgical Management of: (1) Acute Inflammatory Glaucoma; (2) Chronic Simple Glaucoma; (3) Congenital Glaucoma," with Dr. A. Ray Irvine of Los Angeles as the moderator. The Wednesday subject will be "Congenital Cataract" with Dr. Otto Barkan of San Francisco as moderator. The Thursday subject will be "Surgery of the Oblique Muscles" and Dr. C. Allen Dickey of San Francisco will act as the moderator.

OTORHINOLARYNGOLOGY PANEL DISCUSSIONS

Panel discussions in otorhinolaryngology will be held Tuesday, Wednesday, and Thursday mornings from 10:45 to 12:15 o'clock. The Tuesday

subject will be "Rehabilitation of the Hard of Hearing" with Dr. Walter P. Work of San Francisco as moderator. The Wednesday subject will be "The Preparation of the Surgical Patient and Postoperative Care" with Dr. Colby Hall of Los Angeles as moderator. The Thursday subject for discussion will be "Diseases of the Esophagus" with Dr. Alden H. Miller of Los Angeles as moderator.

SPECIALTY PANEL DISCUSSIONS

Specialty panel discussions will be held on Friday afternoon from 1:30 to 3:00 and from 3:15 to 4:45 o'clock, as follows:

Urology—Moderator, Dr. Reed M. Nesbit, Ann Arbor
1:30 to 3:00 p.m.—"The Clinical Management of Branched Renal Calculi."
3:15 to 4:45 p.m.—"Present Day Management of Urinary Tract Infections."

Orthopedic Surgery—Moderator, Dr. John C. Wilson, Los Angeles
1:30 to 3:00 p.m.—"Mechanical Derangements of the Knee Joint."
3:15 to 4:45 p.m.—"Fractures about the Hip."

Thoracic Surgery—Moderator, Dr. Frank S. Dolley, Los Angeles
1:30 to 3:00 p.m.—"Diagnosis and Surgical Treatment by Pulmonary Resection for Carcinoma, Bronchiectasis, and Tuberculosis."
3:15 to 4:45 p.m.—"Surgery of the Esophagus."

Plastic Surgery—Moderator, Dr. Truman G. Blocker, Jr., Galveston
1:30 to 3:00 p.m.—"Congenital Facial Deformities."
3:15 to 4:45 p.m.—"Burn Contractures of the Extremities."

Gynecology and Obstetrics—Moderator, Dr. John C. Burch, Nashville
1:30 to 3:00 p.m.—"Hysterectomy; Physiological Considerations—Indications."
3:15 to 4:45 p.m.—"Hysterectomy, Technical Considerations—Complications."

Neurological Surgery—Moderator, Dr. Howard C. Naffziger, San Francisco
1:30 to 4:45 p.m.—"Cerebral Angiography."
a. "Anatomical Interpretations of Angiography."
b. "Characteristic Patterns of Angiography in Brain Tumors."
c. "Angiography of Circulatory Lesions and Their Treatment."
d. "Technique and Materials."

FORUM ON FUNDAMENTAL SURGICAL PROBLEMS

The Forum on Fundamental Surgical Problems, one of the most popular features of Clinical Congresses during the past few years, will be held on Tuesday through Friday mornings, in two sections meeting concurrently. Brief reports of original clinical and experimental observations relating to the broad aspects of surgery and the surgical specialties will be presented, under the general direction of Dr. Owen H. Wangensteen, chairman of the committee, Forum on Fundamental Surgical Problems.

HOSPITAL CONFERENCES

The opening meeting of the twenty-seventh Hospital Standardization Conference will constitute the first formal session of the Clinical Congress, and will be a General Assembly for both surgeons and hospital representatives. Dr. Arthur W. Allen of Boston, President of the College, will preside. The hospital conferences will continue on Monday afternoon, with sessions following on Tuesday, Wednesday, and Thursday mornings, afternoons and evenings.

Hospital trustees, administrators, heads of the various hospital departments and their personnel, nursing groups, and many other persons directly or indirectly concerned about hospital progress, are invited to participate in the discussions at the hospital conferences, at which leaders in the hospital field are the speakers and the moderators. The meetings will include formal sessions, panel discussions, round table conferences, symposia, and forums.

A meeting which is always of great interest to hospital administrators and members of medical staffs in hospitals, as well as to surgeons, is the Symposium on Graduate Training in Surgery which is scheduled for Thursday afternoon after the Annual Meeting of Fellows.

COMMITTEE ON ARRANGEMENTS

The Committee on Arrangements for the Clinical Congress in Los Angeles has been well organized and is actively functioning. The membership follows:

General Committee

Donald G. Tollefson, M.D., F.A.C.S., *Chairman*
Hugh T. Jones, M.D., F.A.C.S., *Vice-Chairman*
Harold Lincoln Thompson, M.D., F.A.C.S., *Secretary-Treasurer*
Gilbert J. Thomas, M.D., F.A.C.S., *Regent of the College*
E. Vincent Askey, M.D., F.A.C.S.
Max W. Bay, M.D., F.A.C.S.
J. MacKenzie Brown, M.D., F.A.C.S.
Lawrence Chaffin, M.D., F.A.C.S.
A. Ray Irvine, M.D., F.A.C.S.

Maurice Kahn, M.D., F.A.C.S.
W. E. MacPherson, M.D.
B. O. Raulston, M.D.
Louis J. Regan, M.D.
Carl Rusche, M.D., F.A.C.S.
Stafford Warren, M.D.

Committee for the Southern California Chapter

Ray B. McCarty, M.D., F.A.C.S., Riverside
Meredith G. Beaver, M.D., F.A.C.S., Redlands
Clarence E. Rees, M.D., F.A.C.S., San Diego
Carl G. Johnson, M.D., F.A.C.S., Long Beach
James H. Saint, M.D., F.A.C.S., Santa Barbara

Hospital Committee

The members of the hospital committee are listed with the list of hospitals participating in the clinical program which preceded the preliminary schedule of hospital clinics in the June issue.

MEDICAL MOTION PICTURES

An appreciated feature of the Clinical Congress will again be the showing of medical motion pictures each day. The latest available pictures on surgery and related subjects will be presented. Special showings will be arranged of medical motion pictures in the fields of ophthalmology and otorhinolaryngology. Both sound and silent films will be shown, all of which will have been approved by the Committee on Motion Pictures. Some of the newer medical motion pictures now under production will be shown.

TECHNICAL AND SCIENTIFIC EXHIBITIONS

The Technical and Scientific Exhibits will occupy the Ballroom foyer, the Renaissance Room, and the Galleria of the Biltmore Hotel, according to present plans. Leading manufacturers of surgical instruments, x-ray apparatus, sterilizers, operating room lights, ligatures, dressings, hospital apparatus and supplies of all kinds, and pharmaceuticals, and publishers of medical books will be represented.

ADVANCE REGISTRATION

Surgeons who wish to attend the Congress should register in advance. Under a new plan, advance registration will greatly expedite the procedure of registering.

No registration fee will be charged Fellows whose dues are paid to December 31, 1947. For endorsed Junior and Senior Candidates, the fee will be $5.00. Non-Fellows who after individual consideration are permitted to register, will pay a fee of $10.00.

No registration fee will be required of initiates of the class of 1948.

HOTEL RESERVATIONS

It is desirable to make hotel reservations as early as possible because of the shortage of hotel rooms that prevails in Los Angeles as well as in other cities. In making these, communications should be addressed to the Los Angeles Convention and Visitors' Bureau, care of the Los Angeles Chamber of Commerce, stating that you will be attending the Clinical Congress of the American College of Surgeons. All hotel reservations for the Clinical Congress are to clear through this Bureau. No correspondence should be sent directly to the hotels. A form for reservations was enclosed in the letter recently sent to Fellows. Choice of hotels may be designated. The hotels in Los Angeles require a deposit in advance.

There follows the list of member hotels, Convention and Visitors' Bureau, Los Angeles Chamber of Commerce:

LOS ANGELES HOTELS

	Rates (as of May 15, 1948) Subject to change	
	Double	Twin
Alexandria, 210 West 5th St.	$ 6.00 up	$ 7.00 up
Ambassador, 3400 Wilshire Blvd.	$10.00–17.00	$10.00–17.00
Biltmore, 515 South Olive St.	$ 7.50–12.00	$ 7.50–12.00
Chancellor, 3191 West 7th St.	$ 4.50– 6.00	$ 4.50– 6.00
Chapman Park, 3401 Wilshire Blvd.	$ 6.00– 7.00	$ 7.00– 8.00
Clark, 426 South Hill St.	$ 4.50– 5.00	$ 5.50– 6.00
Commodore, 1203 West 7th St.	$ 3.00– 3.50	$ 4.00
Elmar, 235 South Hope St.	$ 3.00	$ 3.00
Figueroa, 939 South Figueroa St.	$ 3.00– 4.00	$ 5.00
Gates, 5th and Figueroa Sts.	$ 3.50– 6.00	$ 3.50– 6.00
Gaylord, 3355 Wilshire Blvd	$ 7.50 up	$ 7.50 up
Hayward, 6th and Spring Sts.	$ 5.00	$ 5.50
Hollywood Drake, 6724 Hollywood Blvd.	$ 3.50 up	$ 4.50 up
Hollywood Hotel, Hollywood at Highland.	$ 5.00– 6.00	$ 5.00– 6.00
Hollywood Knickerbocker, 1014 Ivar St.	$ 6.00 up	$ 6.00
Hollywood Plaza, 1637 No. Vine St.	$ 4.00 up	$ 4.50 up
Hollywood Roosevelt, 7000 Hollywood Blvd.	$ 7.00 up	$ 8.00 up
Kipling, 4077 West Third St.	$ 3.00	$ 3.50– 4.00
Lankershim, 230 West 7th St.	$ 3.00– 4.50	$ 4.50– 7.00
Mayan, 3049 West 8th St.	$ 4.00– 5.50	$ 5.00– 5.50
Mayfair, 1256 West 7th St.	$ 5.00 up	$ 6.00– 7.00
Natick, 108 West 1st St.		
Rosslyn, 111 West 5th St.	$4.00– 8.00	$4.50– 9.00
San Carlos, 507 West 5th Street	$ 4.50	$ 6.00
Savoy, 6th St. and Grand Ave.	$ 3.50– 5.50	$ 4.50– 5.00
Town House, 639 Commonwealth Ave.	$14.00	$14.00